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(54) **PREDICTING POST-TREATMENT SURVIVAL IN CANCER PATIENTS WITH MICRORNAS**

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C12P 19/34 (2006.01)

(52) **U.S. Cl.** **435/6**; 435/91.1; 435/91.2

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

This invention provides a method for predicting the post-treatment survival prospect of a cancer patient based on the expression level(s) of microRNAs hsa-miR137, hsa-miR372, hsa-miR182*, hsa-miR221, and hsa-let-7a in that cancer patient.

6 Claims, 3 Drawing Sheets

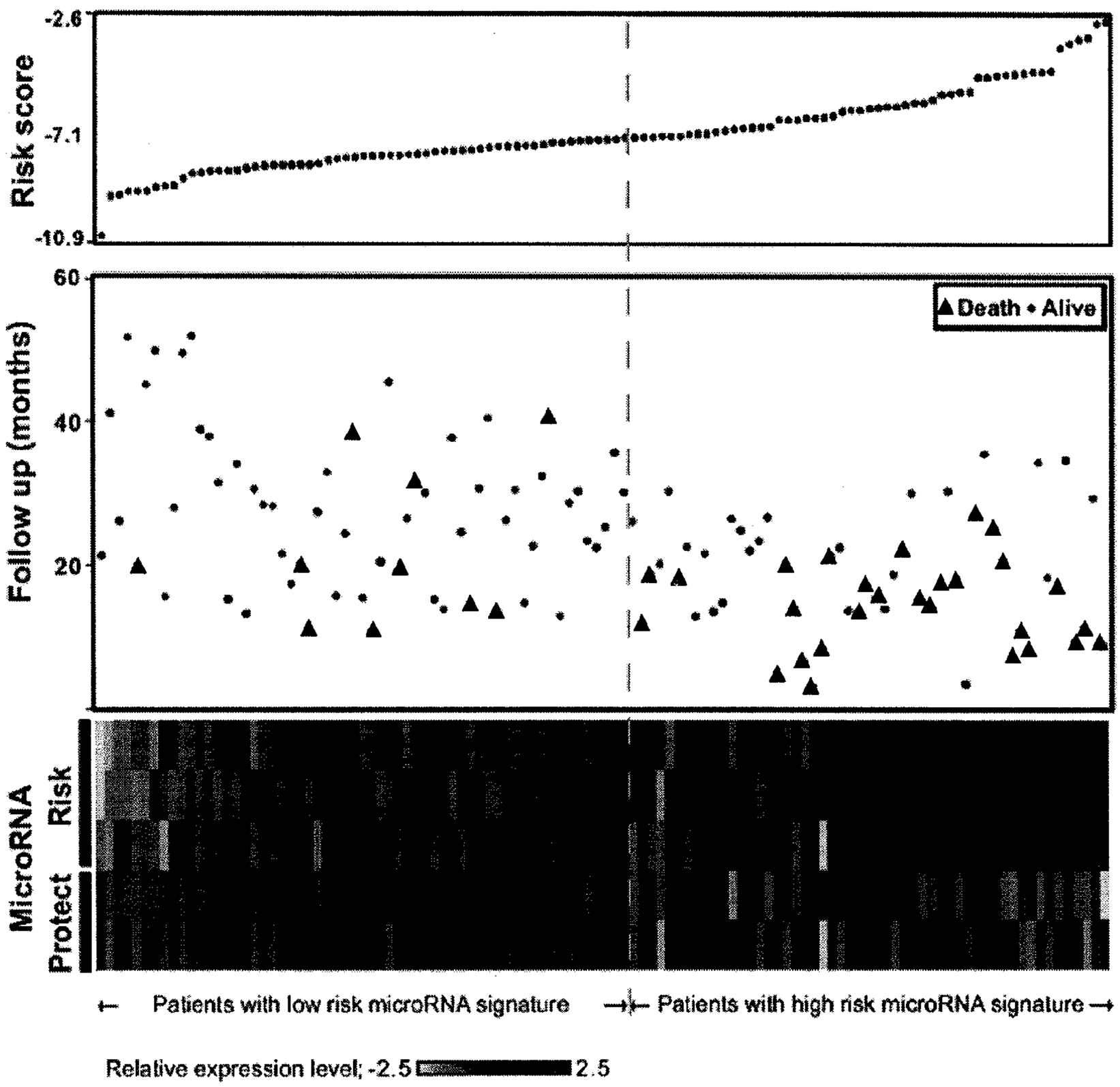
Risk score
-2.6
-7.1
-10.9
Follow up (months)
60
40
20
Death
Alive
MicroRNA
Risk
Protect
← Patients with low risk microRNA signature →← Patients with high risk microRNA signature →
Relative expression level; -2.5 2.5

FIGURE 1

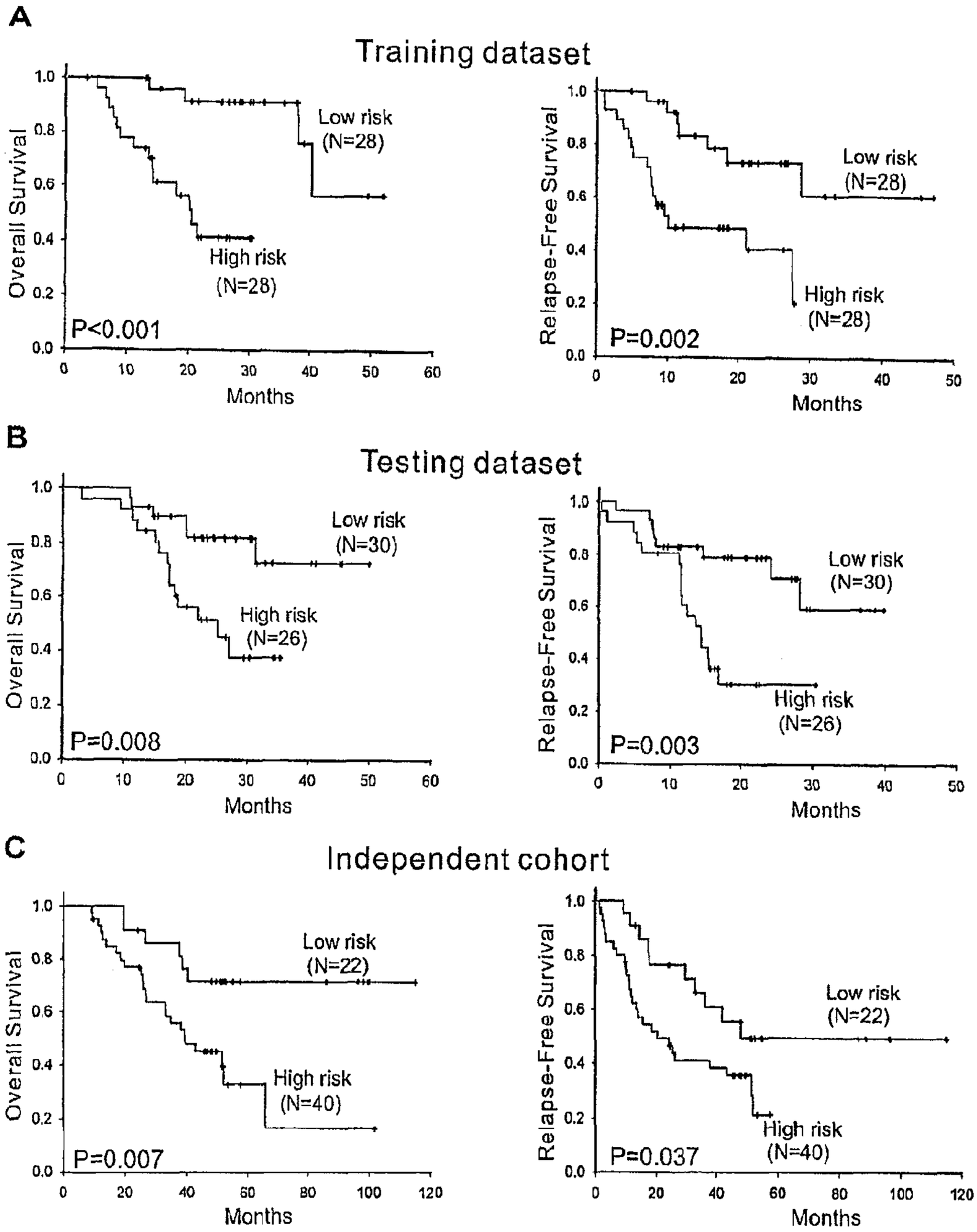
A
Training dataset
Overall Survival
Low risk
(N=28)
High risk
(N=28)
P<0.001
Months
Relapse-Free Survival
Low risk
(N=28)
High risk
(N=28)
P=0.002
Months
B
Testing dataset
Overall Survival
Low risk
(N=30)
High risk
(N=26)
P=0.008
Months
Relapse-Free Survival
Low risk
(N=30)
High risk
(N=26)
P=0.003
Months
C
Independent cohort
Overall Survival
Low risk
(N=22)
High risk
(N=40)
P=0.007
Months
Relapse-Free Survival
Low risk
(N=22)
High risk
(N=40)
P=0.037
Months

FIGURE 2

Figure 3

A
Stage I
Overall Survival
Low risk (N=31)
All (N=47)
High risk (N=16)
P =0.044
Months
Relapse-Free Survival
Low risk (N=31)
All (N=47)
High risk (N=16)
P =0.031
Months
B
Stage II
Overall Survival
Low risk (N=15)
All (N=28)
High risk (N=13)
P =0.047
Months
Relapse-Free Survival
Low risk (N=15)
All (N=28)
High risk (N=13)
P =0.046
Months
C
Stage III
Overall Survival
Low risk (N=12)
All (N=37)
High risk (N=25)
P =0.004
Months
Relapse-Free Survival
Low risk (N=12)
All (N=37)
High risk (N=25)
P =0.076
Months
D
Adenocarcinoma
Overall Survival
Low risk (N=23)
High risk (N=32)
P =0.006
Months
Relapse-Free Survival
Low risk (N=23)
High risk (N=32)
P =0.010
Months
E
Squamous cell carcinoma
Overall Survival
Low risk (N=31)
High risk (N=19)
P =0.005
Months
Relapse-Free Survival
Low risk (N=31)
High risk (N=19)
P =0.075
Months

PREDICTING POST-TREATMENT SURVIVAL IN CANCER PATIENTS WITH MICRORNAS

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 60/910,993, filed on Apr. 10, 2007, the contents of which are hereby incorporated by reference in its entirety.

BACKGROUND

Lung cancer, predominantly non-small-cell lung cancer (NSCLC), is the most common cause of cancer deaths worldwide. See Jemal et al., CA Cancer J. Clin. 56:106-130 (2006). Early-stage NSCLC patients show a relapse rate of 40% within 5 years after treatment; it is suggested that the disease stage might be a factor associated with clinical outcomes. See Miller, Am. J. Respir. Cell Mol. Biol. 33: 216-223 (2005). However, this factor alone is inadequate to predict such outcomes.

It has been suggested that gene expression profiling, in particular, microRNA profiling, is useful in both cancer diagnosis and prognosis. See Endoh et al., J. Clin. Oncol. 22:811-819 (2004); and Potti et al., N. Engl. J. Med. 355:570-580 (2006). For example, the expression patterns of certain microRNAs are found to be more accurate than the expression patterns of protein-coding genes in determining cancer subtypes. See Calin et al., Nat. Rev. Cancer 6:857-866 (2006); and Volinia et al., Proc. Natl. Acad. Sci. U.S.A. 103: 2257-2261 (2006).

MicroRNAs are small non-protein-coding RNAs that regulate the expression of hundreds of genes post-transcriptionally via RNA interference, thereby controlling a broad range of biopathways, e.g., cell proliferation, differentiation, and apoptosis. See Calin et al., 2006. Certain microRNA signatures, i.e., one or more microRNAs that display particular expression patterns in a group of patients, were reported to be associated with clinical outcomes of chronic lymphocytic leukemia, lung adenocarcinoma, breast, pancreas and cancers. See Calin et al., 2006. Identifying new microRNA signatures is of great interest, as they would be useful tools in predicting clinical outcomes of various cancers, in particular, NSCLC.

SUMMARY

This invention is based on the observation that the expression levels of certain microRNAs, such as hsa-miR137, hsa-miRNA372, hsa-miR182*, hsa-miR221 and hsa-let-7a, correlate with the post-treatment survival prospect of a cancer patient.

In one aspect, this invention provides a method for predicting post-treatment survival prospect of a cancer patient by determining a normalized threshold cycle value (−dCt) based on the expression level of hsa-miR137, hsa-miR372, hsa-miR182*, hsa-miR221, or hsa-let-7a. The patient is determined to have a fair prospect of post-treatment survival if the −dCt value of hsa-miR137, hsa-miR182*, and hsa-miR372 is equal to or lower than −8.22, −7.83, and −11.25, respectively, or if the −dCt value of hsa-miR221 and hsa-let-7a is equal to or higher than −0.57 and 2.21, respectively.

In another aspect, the post-treatment survival prospect of a cancer patient can be predicted based on the expression levels of four of the microRNAs selected from hsa-miR137, hsa-miR372, hsa-miR182*, hsa-miR221 and hsa-let-7a. More specifically,

1. When the expression levels of hsa-miR372, hsa-miR182*, hsa-miR221 and hsa-let-7a are investigated, a risk score is calculated as follows: (0.31×expression level of hsa-miR372)+(0.28×expression level of hsa-miR182*)+(−0.13×expression level of hsa-miR221)+(−0.14×expression level of hsa-let-7a). A risk score equal to or lower than −5.90 indicates that the patient has a fair prospect for post-treatment survival.

2. When the expression levels of hsa-miR137, hsa-miR182*, hsa-miR221 and hsa-let-7a are investigated, a risk score is calculated as follows: (0.15×expression level of hsa-miR137)+(0.28×expression level of hsa-miR182*)+(−0.13×expression level of hsa-miR221)+(−0.14×expression level of hsa-let-7a). A risk score equal to or lower than −3.71 indicates that the patient has a fair prospect for post-treatment survival.

3. When the expression levels of hsa-miR137, hsa-miR372, hsa-miR221 and hsa-let-7a are investigated, a risk score is calculated as follows: (0.15×expression level of hsa-miR137)+(0.31×expression level of hsa-miR372)+(−0.13×expression level of hsa-miR221)+(−0.14×expression level of hsa-let-7a). A risk score equal to or lower than −4.87 indicates that the patient has a fair prospect for post-treatment survival.

4. When the expression levels of hsa-miR137, hsa-miR182*, hsa-miR372 and hsa-let-7a are investigated, a risk score is calculated as follows: (0.15×expression level of hsa-miR137)+(0.28×expression level of hsa-miR182*)+(0.31×expression level of hsa-miR372)+(−0.14×expression level of hsa-let-7a). A risk score equal to or lower than −7.02 indicates that the patient has a fair prospect for post-treatment survival.

5. When the expression levels of hsa-miR137, hsa-miR182*, hsa-miR221 and hsa-miR372 are investigated, a risk score is calculated as follows: (0.15×expression level of hsa-miR137)+(0.28×expression level of hsa-miR182*)+(−0.13×expression level of hsa-miR221)+(0.31×expression level of hsa-miR372). A risk score equal to or lower than −6.86 indicates that the patient has a fair prospect for post-treatment survival.

In yet another aspect, the post-treatment survival prospect of a cancer patient can be predicted based on his or her expression levels of the five microRNAs mentioned above. A risk score is calculated as follows: (0.15×expression level of hsa-miR137)+(0.31×expression of hsa-miR372)+(0.28×expression level of hsa-miR182*)+(−0.13×expression level of hsa-miR221)+(−0.14×expression level of hsa-let-7a). A cancer patient has fair prospect of post-treatment survival if his or her risk score is equal to or lower than −7.1.

In still another aspect, the post-treatment survival prospect can be predicted based on the expression levels of hsa-miR221, hsa-miR372, and hsa-miR137. A risk score is calculated as follows: (0.15×expression level of hsa-miR137)+(0.31×expression of hsa-miR372)+(−0.13×expression level of hsa-miR221). A cancer patient will have a fair prospect of post-treatment survival if the risk score is equal to or lower than −4.7.

A cancer patient having "a fair prospect of post-treatment survival" means that his or her risk of post-treatment death is at least 50% (e.g., 100% or 150%) lower than the average risk of death in patients having the same type of cancer.

Also within the scope of this invention is a kit for detecting the expression of microRNAs. In one example, the kit comprises oligonucleotides capable of detecting the expression of hsa-miR221, hsa-miR372, and hsa-miR137. In another example, it comprises oligonucleotides capable of detecting the expression of at least four microRNAs selected from hsa-miR137, hsa-miR372, hsa-miR182*, hsa-miR221, and hsa-let-7a. The oligonucleotides contained in any of the just-described kits can be immobilized on a supporting member (e.g., a polymer substrate) to form nucleic acid chips.

The cancer patient who has been subjected to treatment (e.g., surgical treatment, chemical treatment, or radiotherapy) has lung cancer (e.g., non-small cell lung cancer of all stages), leukemia, breast cancer, pancreatic cancer, adenocarcinoma, or squamous cell carcinoma, colon cancer or hepatocellular carcinoma.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and from the claims.

DESCRIPTION OF DRAWINGS

FIG. **1** is a diagram showing a microRNA risk-score analysis of 112 NSCLC patients based on the expression levels of hsa-miR137, hsa-miR372, hsa-miR182*, hsa-miR221, and hsa-let-7a in these patients. Upper panel: MicroRNA risk-score distribution. Middle panel: Patients' death/survival status. Bottom panel: Patients' microRNA expression profiles; the five rows, from bottom to top, refer to hsa-let-7a, hsa-miR221, hsa-miR372, hsa-miR182*, and hsa-miR137, respectively; the columns each represent a patient. The dotted line represents the cut-off line (risk score −7.1) dividing patients into low-risk and high-risk groups.

FIG. **2** is a diagram showing Kaplan-Meier estimates of the overall survival and relapse-free survival of the NSCLC patients in both low-risk and high-risk groups. Panel A shows results obtained from 56 patients in a training dataset; Panel B shows results obtained from 56 patients in a testing dataset; and Panel C shows results obtained from 62 patients in an independent cohort.

FIG. **3** is a diagram showing Kaplan-Meier estimates of the overall survival and relapse-free survival of NSCLC patients in both low-risk and high-risk groups. Panel A shows results obtained from state I NSCLC patients (n=47); Panel B shows results obtained from stage II NSCLC patients (n=28); Panel C shows results obtained from stage III NSCLC patients (n=37); Panel D shows results obtained from adenocarcinoma patients (n=55); and Panel E shows results obtained from squamous cell carcinoma patients (n=50).

DETAILED DESCRIPTION

This application provides a method for predicting a clinical outcome (e.g., the post-treatment survival prospect) of a cancer patient based on the expression patterns of one or more microRNAs that are associated with the clinical outcome.

The one or more microRNAs associated with the outcome can be identified as follows.

A group of post-treatment cancer patients are recruited. These patients, suffering from the same type of cancer, are randomly assigned to a training group and a testing group. The expression levels of a number of microRNAs in cancer tissues/cells (e.g., contained in biopsies, formalin-fixed-paraffin-embedded tissues, or frozen tissues) are determined for the patients in both groups following methods known in the art, e.g., real-time PCR or micro-array analysis. The expression level of each microRNA thus determined is normalized by the expression level of an internal control, such as a small nuclear RNA (e.g., U1, U2, or U6), in the same patient to obtain a normalized expression level.

Normalized expression levels of the microRNAs obtained from the training group are subjected to statistical analysis, e.g., Cox regression analysis, to determine which microRNA (s) is associated with a clinical outcome (e.g., post-treatment survival) of the cancer patients. In one example, hazard ratios obtained from univariate Cox regression analysis are used to identify the microRNA(s) that is associated with death due to recurrence of cancer or any other cause. See Cox, J. Royal Statistical Society Series B 34:187-220 (1972). If the hazard ratio of a microRNA is less than 1, that microRNA is deemed as a protective microRNA, and if the hazard ratio of a microRNA is greater than 1, that microRNA is deemed as a risk microRNA.

Once the microRNAs associated with a clinical outcome (e.g., protective and risk microRNAs) are identified, the correlation between their expression patterns and a clinical outcome can be determined by statistical analysis known in the art. In one example, a risk score is calculated for each patient based on the expression levels of one or more of the protective and/or risk microRNAs, and a relationship between the value of the risk score and a patient's survival period after treatment is then determined. The correlation thus determined is verified in the testing group to confirm that the microRNA expression pattern is truly associated with the clinical outcome of interest. Preferably, this correlation is further validated in an independent cohort including a number of patients having the same type of cancer as those in the training and testing groups.

After verification, and preferably, validation, the identified microRNAs can be used to predict the clinical outcome, based on their expression patterns, in patients having the same type of cancer. For example, one can construct a mathematical formula, taking into consideration both the expression levels of these microRNAs and the significance of the statistical analysis mentioned above. Following this mathematical formula, a risk score is calculated for a patient. The value of the risk score indicates the patient's clinical outcome.

The microRNAs associated with a clinical outcome of a cancer patient can also be used to identify potential targets for cancer treatment. See Czech, N. Engl. J. Med. 354:1194-1195 (2006). Genes targeted by these microRNAs can be identified using microRNA target prediction algorithms, e.g., PicTar, see Krek et al., Nat. Genet. 37:495-500 (2005); TargetScan, see Lewis et al., Cell 115:787-798 (2003); miRNAMap, see Hsu et al., Nucleic Acids Res. 34:D135-139 (2006); miRBase, see Griffiths-Jones et al., Nucleic Acids Res. 34:D140-144 (2006); GenMAPP, see genmapp.org; and Reactome, see reactome.org. These genes and their products are potential targets or agents for cancer therapy.

Without further elaboration, it is believed that the above description has adequately enabled the present invention. The example below shows microRNA signatures that can be used for predicting post-treatment survival prospect in NSCLC patients. This example is to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. All of the publications cited herein are hereby incorporated by reference in their entirety.

Materials and Methods

(a) Patients and Tissue Specimens.

112 consecutive NSCLC patients, all underwent surgical resection, were recruited from the Taichung Veterans General Hospital. These patients were randomly assigned to a training dataset (n=56) and a testing dataset (n=56). In addition, 62 consecutive patients who also underwent surgical resection were recruited from National Taiwan University Hospital. These 62 patients formed an independent cohort. Frozen specimens of lung cancer tissues were obtained from all of the patients recruited for this study. All of the patients are Han Chinese.

(b) MicroRNA Profiling.

MicroRNA expression profiling was performed using ABI PRISM 7900 Real Time PCR System and TaqMan

MicroRNA Assays Human Panel-Early Access Kit, which contains primers for determining 157 mature human microRNAs (Applied Biosystems). The cDNA of each microRNAs was first amplified using TaqMan MicroRNA RT reagent and primers specific for that microRNA, and further amplified using TaqMan 2× Universal PCR Master mix. During amplification, a fluorescent dye was incorporated into the cDNA product. The expression level of each microRNA, represented by a threshold cycle (Ct) value, was determined based on the level of the fluorescence generated by the fluorescent dye incorporated into the cDNA product. Ct refers to the fractional number at which the fluorescence passes a fixed threshold. The Ct value of each microRNA was then normalized by that of U6, a common internal control for microRNA quantification assays. See Jiang et al., Nucleic Acids Res. 33:5394-5403 (2005); and Yanaihara et al., Cancer Cell 9:189-198 (2006). More specifically, the normalized Ct value (−dCt) was calculated as follows: $-dCt=(Ct_{microRNA}-Ct_{U6})$.

(c) Statistical Analysis

Hazard ratios obtained from univariate Cox regression analysis were used to identify the microRNA(s) whose expression levels were associated with patient's post-treatment death/survival. To reduce false positive results, the P value of univariate Cox regression value of each microRNA was evaluated by a permutation test, wherein a patient's survival period, together with censoring status, was randomly permuted for a total of 10,000 iterations.

A mathematical formula was constructed for calculating a risk store for each patient. The formula took into account both the expression levels of one or more of the microRNAs that were identified to be associated with post-treatment death/survival and the regression coefficients derived from the aforementioned univariate Cox regression analyses. See Lossos et al., N. Engl. J. Med. 350:1828-1837; and Cox, 1972. The risk score of a patient correlates with the patient's post-treatment survival period: patients having high risk scores are expected to have shorter survival periods after treatment and patients having low risk scores are expected to live longer after treatment.

All of the patients subjected to this study were assigned to a high-risk group and a low-risk group based on their risk scores. The differences in patient characteristics between the high-risk group and the low-risk group were analyzed using Student's t test for continuous variables or Fisher's exact test for categorical variables. The Kaplan-Meier method was used to estimate the overall survival and relapse-free survival for patients in both groups. The differences as to the overall and replapse-free survival between patients in the two groups were analyzed using the log-rank test. All results thus obtained from the training dataset were validated in patients in the testing dataset and patients in the independent cohort.

Multivariate Cox proportional hazard regression analysis and stepwise variable selection were conducted to evaluate the contribution of independent prognostic factors associated with patient survivals. The microRNA signature risk-score, age, sex, stage and histology were used as covariates. All analyses were performed using SAS version 9.1 software (SAS Institute Inc). Two-tailed tests and P values <0.05 indicates that results are statistically significant.

More details of performing the methods described above can be found in Yu et al., Cancer Cell 13, 48-57 (2008).

Results

(a) Identification and Verification of a MicroRNA Signature for Predicting the Overall Survival and Relapse-Free Survival of NSCLC Patients

Table 1 below shows the clinical characteristics of the 56 NSCLC patients assigned to the training dataset and the 56 NSCLC patients assigned to the testing dataset. There was no significant difference between patients in these two datasets with respect to their clinical characteristics.

The expression levels of microRNAs were determined in all of these patients following the method described above. Results obtained from the training dataset were subjected to univariate Cox regression analysis to identify the microRNAs whose expression levels were associated with post-treatment death/survival. Five microRNAs, i.e., hsa-miR137, hsa-miR372, hsa-miR182*, hsa-miR221, and hsa-let-7a, were found to be associated with overall survival of the patients in the training dataset. Among them, the former three are high-risk microRNAs and the latter two are protective microRNAs.

Based on the expression levels of these five microRNAs, a patient's risk score was calculated following the formula: (0.15×expression level of hsa-miR-137)+(0.31× expression level of hsa-miR-372)+(0.28×expression level of hsa-miR182*)+(−0.13× expression level of hsa-miR-221)+(−0.14×expression level of hsa-let-7a). Patients having a risk score higher than −7.1 were assigned to a high-risk group and patients having a risk score lower than −7.1 were assigned to a low-risk group.

TABLE 1

Clinicopathologic Characteristics of 112 NSCLC Patients

Characteristic	Training dataset No. of patients (%) n = 56	Testing dataset No. of patients (%) n = 56	P value
Age (mean ± SD)	66.5 ± 10.0	65.3 ± 14.1	0.606†
Gender			
Male	45 (80)	43 (77)	0.818‡
Female	11 (20)	13 (23)	
Stage			
I	21 (38)	26 (46)	0.549‡
II	14 (25)	14 (25)	
III	21 (37)	16 (29)	
Cell type			
Adenocarcinoma	25 (45)	30 (53)	0.150‡
Squamous cell carcinoma	25 (45)	25 (45)	
Others	6 (10)	1 (2)	

†t test.

‡Fisher's exact test.

The clinical characteristics of the patients in both high-risk and low-risk groups are summarized in Table 2 below.

TABLE 2

Clinical Characteristics of NSCLC Patients in Both The High-Risk and Low-Risk Datasets

Characteristic	Patients in high-risk group	Patients in low-risk group	P value
Training dataset (n = 56)	n = 28	n = 28	
Age (mean ± SD)	65.7 ± 10.3	67.3 ± 9.7	0.549†
Gender			
Male	21 (75)	24 (86)	0.503‡
Female	7 (25)	4 (14)	
Stage			
I	5 (18)	16 (57)	0.008‡
II	8 (28)	6 (22)	
III	15 (54)	6 (21)	
Cell type			
Adenocarcinoma	15 (54)	10 (36)	0.353‡
Squamous cell carcinoma	10 (36)	15 (54)	
Others	3 (10)	3 (10)	
Testing dataset (n = 56)	n = 26	n = 30	
Age (mean ± SD)	66.5 ± 13.6	64.3 ± 14.7	0.57†
Gender			
Male	22 (85)	21 (70)	0.224‡
Female	4 (15)	9 (30)	
Stage			
I	11 (42)	15 (50)	0.340‡
II	5 (19)	9 (30)	
III	10 (39)	6 (20)	
Cell type			
Adenocarcinoma	17 (65)	13 (43)	0.179‡
Squamous cell carcinoma	9 (35)	16 (53)	
Others	0 (0)	1 (4)	
Independent cohort (n = 62)	n = 40	n = 22	
Age (mean ± SD)	62.9 ± 10.3	64.1 ± 9.1	0.634†
Gender			
Male	32 (80)	10 (45)	0.010‡
Female	8 (20)	12 (55)	
Stage			
I	15 (37)	13 (59)	0.152‡
II	6 (15)	4 (18)	
III	19 (48)	5 (23)	
Cell type			
Adenocarcinoma	21 (52)	9 (41)	0.563‡
Squamous cell carcinoma	13 (33)	8 (36)	
Others	6 (15)	5 (23)	

†t test.

‡Fisher's exact test.

FIG. **1** shows the risk stores, survival status, and microRNA expression profiles of the NSCLC patients in both the training and testing datasets. Patients having high risk scores express high levels of any of the three high-risk microRNAs and low levels of any of the two protective microRNAs. To the contrary, patients having low risk stores express low levels of any of the high-risk microRNAs and high levels of any of the protective microRNAs.

In the training dataset, the patients in the high-risk group showed shorter post-survival periods than those in the low-risk group. See FIG. **2**, Panel A. The median overall survival period of patients in the high-risk group was about 20 month, while that of patients in the low-risk group was longer than 50 months. As to the median relapse-free survival period, it was about 10 month in the high-risk group and longer than 45 months in the low-risk group. See FIG. **2**, Panel A. These results indicate that the expression pattern of the five microRNAs mentioned above (i.e., a microRNA signature), based on which a patient is assigned either to the high-risk or the low-risk group, is associated with a cancer patient's post-treatment survival period.

The just-mentioned association between the microRNA signature and survival prospect was verified in the testing dataset. Similar to the results obtained from the training dataset, results obtained from the testing dataset also showed that the patients in the low-risk group lived much longer after

treatment than the patients in the high-risk group. See FIG. **2**, Panel B. In the high-risk group, the median overall survival period was about 25 month, and the median relapse-free survival period was about 14 month. In the low-risk group, the median overall survival period and relapse-free survival period were longer than 50 months and longer than 40 month, respectively. All these results were statistically significant.

Multivariate Cox regression analysis showed that, among the factors listed in Table 3 below, this microRNA signature was the only factor associated with the overall survival (hazard ratio [HR]=10.31, P=0.002) in NSCLC patients.

TABLE 3

Multivariate Cox Regression* Analysis of The MicroRNA Signature and Survivals in NSCLC Patients

Variable	Hazard ratio	95% CI	P value
Overall survival			
Training dataset (n = 56)			
microRNA expression signature	10.31	2.33 to 45.56	0.002
Testing dataset (n = 56)			
microRNA expression signature	3.65	1.29 to 10.37	0.015
Stage	8.12	2.83 to 23.25	<0.001
Age	1.08	1.03 to 1.14	0.002
Independent cohort (n = 62)			
microRNA expression signature	2.81	1.13 to 7.01	0.026
Stage	2.35	1.13 to 4.89	0.022
Relapse-free survival			
Training dataset (n = 56)			
microRNA expression signature	3.29	1.24 to 8.71	0.016
Stage	2.63	1.10 to 6.25	0.029
Testing dataset (n = 56)			
microRNA expression signature	2.86	1.20 to 6.82	0.018
Stage	2.97	1.32 to 6.69	0.009
Independent cohort (n = 62)			
microRNA expression signature	2.39	1.12 to 5.10	0.024
Stage	2.76	1.43 to 5.34	0.003
Age	0.93	0.90 to 0.97	<0.001

*Variables were selected through stepwise selection method

(b) Validation of the microRNA Signature for Survival Prediction in an Independent Cohort

The microRNA signature mentioned above was validated for its use in predicting post-treatment survival prospect in an independent cohort, including 62 NSCLC patients.

The clinical characteristics of the 62 patients are summarized in Table 2 above. The risk score of each patient was calculated based on his or her expression patterns of the five microRNAs following the method described above. The patients having risk scores higher than −7.1 were assigned to a high-risk group and the patients having risk scores below −7.1 were assigned to a low-risk group. As shown in FIG. **2**, Panel C, the patients in the high-risk group had shorter post-treatment survival periods than those in the low-risk group, i.e., 40 months versus longer than 120 months in terms of median overall survival period and 20 months versus 48 months in terms of median relapse-free survival period. See FIG. **2**C. Multivariate Cox regression analysis showed that microRNA signature and stage were associated with overall survival and relapse-free survival (see Table 3 supra).

These results confirm that the microRNA signature can be used in predicting a cancer patient's post-treatment survival prospect.

(c) Association between the MicroRNA Signature and Post-Treatment Survival of NSCLC Patients in Different Disease Stages and Histological Subgroups

NSCLC patients in different disease stages and in different histological subgroups were assigned to high-risk and low-risk groups based on their microRNA signature following the method described above. As shown in FIG. **3**, the patients in the low-risk groups lived longer after treatment than the patients in the high-risk groups. See Panels A-E. These results indicate that the microRNA signature can also be used to predict the post-treatment survival prospect for NSCLC patients in different disease stages, i.e., stage I, II or III, and in different histological sub-groups, i.e., adenocarcinoma or squamous cell carcinoma sub-groups.

(d) MicroRNA Signatures as Predictors of Patient Survival in NSCLC

Univariate Cox regression analysis showed that the expression level of each of the 5 microRNAs, i.e., hsa-miR137, hsa-miR372, hsa-miR182*, hsa-miR221, or hsa-let-7a, was associated with NSCLC survival. See Table 4 below. The log-rank analysis showed that the microRNA signature composed of all of the five microRNAs is the optimal predictor for patient survival. See also Table 4 below.

In addition, univariate Cox regression analysis showed that a microRNA signature composed of any four of the aforementioned five microRNAs was also associated with patient post-treatment survival. See Table 5 below.

TABLE 4

The P values of log-rank test in Kaplan-Meier survival analysis of the 5-microRNA signature compared to individual microRNA expression in NSCLC patients

microRNA*	Training dataset	Testing dataset	Independent cohort
	Overall survival		
All five microRNAs	<0.001	0.008	0.007
hsa-miR-221	0.021	0.264	0.955
hsa-let-7a	0.906	0.292	0.356
hsa-miR-137	0.026	0.347	0.005
hsa-miR-372	0.358	0.011	<0.001
hsa-miR-182*	0.126	0.005	0.904
	Relapse-free survival		
All five microRNAs	0.002	0.003	0.037
hsa-miR-221	0.008	0.680	0.751
hsa-let-7a	0.258	0.225	0.461
hsa-miR-137	0.086	0.619	0.007
hsa-miR-372	0.615	0.005	0.003
hsa-miR-182*	0.343	0.005	0.961

*two groups were separated based on median

TABLE 5

The P values of Log-Rank Test in Kaplan-Meier Survival Analysis of The 5-microRNA Signature Versus 4-microRNA Signatures in NSCLC Patients

	Training dataset	Testing dataset	Independent cohort
	Overall survival		
All five microRNAs	<0.001	0.008	0.007
Four of the five microRNAs			
hsa-miR137, hsa-miR372, hsa-miR182*, and hsa-let-7a	<0.001	0.007	0.022
hsa-miR137, hsa-miR372, hsa-miR182*, and hsa-miR221	0.001	0.006	0.057
hsa-miR372, hsa-miR182*, hsa-miR221, and hsa-let-7a	0.020	0.038	0.058
hsa-miR137, hsa-miR182*, hsa-miR221, and hsa-let-7a	0.022	0.141	0.100
hsa-miR137, hsa-miR372, hsa-miR221, or hsa-let-7a	<0.001	0.204	0.003
	Relapse-free survival		
All five microRNAs	0.002	0.003	0.037
Four of the five microRNAs			
hsa-miR137, hsa-miR372, hsa-miR182*, and hsa-let-7a	0.012	0.013	0.078
hsa-miR137, hsa-miR372, hsa-miR182*, and hsa-miR221	0.033	0.008	0.154
hsa-miR372, hsa-miR182*, hsa-miR221, and hsa-let-7a	0.139	0.006	0.189
hsa-miR137, hsa-miR182*, hsa-miR221, and hsa-let-7a	0.037	0.441	0.116
hsa-miR137, hsa-miR372, hsa-miR221, or hsa-let-7a	<0.001	0.048	0.015

(e) Putative Gene Targets of microRNAs

GeneSpring pathway annotated software (Silicon Genetics) was applied to predict the putative pathways that the five microRNAs might be involved and the results thus obtained are summarized in Tables 6 and 7 below.

TABLE 6

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
let-7a	ABCB9	Hs.511951	4	ABC transporters - General 02010	GO: 6857 GO: 15031 GO: 7283	GO: 5524 GO: 16887 GO: 42626 GO: 166 GO: 15198 GO: 5215	GO: 43190 GO: 5783 GO: 16021 GO: 5764
let-7a	ABCC10	Hs.55879	4	ABC transporters - General 02010	GO: 6810	GO: 5524 GO: 16887 GO: 42626 GO: 166	GO: 16021
let-7a	ABCC5	Hs.368563	4	ABC transporters - General 02010	GO: 6810	GO: 5524 GO: 16887 GO: 42626 GO: 15239 GO: 166 GO: 8514	GO: 16021 GO: 5887 GO: 5624
let-7a	ATP2A2	Hs.506759	4	Calcium signaling pathway 04020	GO: 6816 GO: 6812 GO: 7155 GO: 8544 GO: 8152 GO: 15992	GO: 5524 GO: 48155 GO: 5509 GO: 5388 GO: 16787 GO: 16820 GO: 287 GO: 166	GO: 5887 GO: 16020 GO: 5624 GO: 5792 GO: 16529
let-7a	BZW1	Hs.355983	4		GO: 6446	GO: 3743	

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
let-7a	CDC25A	Hs.1634	4	Cell cycle 04110; Cell Cycle 69278; Cell Cycle Checkpoints 69620	GO: 51301 GO: 8283 GO: 7067 GO: 6470 GO: 79	GO: 16787 GO: 4725	GO: 8372 GO: 5622
let-7a	CHD4	Hs.162233	4		GO: 6333 GO: 16568 GO: 7001) GO: 6357 GO: 6350	GO: 5524 GO: 4003 GO: 3677 GO: 3682 GO: 16787 GO: 46872 GO: 166 GO: 5515 GO: 8270	GO: 785 GO: 5634
let-7a	CHD9	Hs.59159	4		GO: 6333	GO: 5524 GO: 3677 GO: 3682 GO: 4386	GO: 785 GO: 16021 GO: 5634
let-7a	CHRD	Hs.166186	4	TGF-beta signaling pathway 04350	GO: 7275 GO: 1501	GO: 5554	GO: 8372
let-7a	DHX57	Hs.468226	4				
let-7a	DTX2	Hs.187058	4	Notch signaling pathway 04330	GO: 7219 GO: 16567	GO: 46872 GO: 4842 GO: 8270	GO: 5634 GO: 151
let-7a	E2F5	Hs.445758	4	Cell cycle 04110; TGF-beta signaling pathway 04350; Cell Cycle 69278	GO: 74 GO: 6355 GO: 6350	GO: 5515 GO: 3700	GO: 5634 GO: 5667
let-7a	EZH2	Hs.444082	4		GO: 6325 GO: 6355 GO: 6350	GO: 3677	GO: 5634
let-7a	FASLG	Hs.2007	4	Apoptosis 04210; Cytokine-cytokine receptor interaction 04060; MAPK signaling pathway 04010; Natural killer cell mediated cytotoxicity 04650; Type I diabetes mellitus 04940; Apoptosis 109581	GO: 6915 GO: 7267 GO: 6955 GO: 6917 GO: 43123 GO: 7165	GO: 5164	GO: 5615 GO: 5887 GO: 16020
let-7a	GALE	Hs.557524	4	Galactose metabolism 00052; Nucleotide sugars metabolism 00520; Metabolism of sugars 71387	GO: 5975 GO: 6012 GO: 9225	GO: 51287 GO: 3978 GO: 3824 GO: 16853	
let-7a	GIPC1	Hs.6454	4	mRNA processing	GO: 7186	GO: 5515 GO: 5102	GO: 5829 GO: 16020 GO: 5624 GO: 5625
let-7a	GOLT1B	Hs.62275	4		GO: 43123 GO: 16192	GO: 4871	GO: 16021
let-7a	HOXC11	Hs.127562	4		GO: 7275 GO: 7492 GO: 6355	GO: 3702 GO: 3700	GO: 5634
let-7a	IDH2	Hs.513141	4	Krebs-TCA Cycle; Citrate cycle; Glutathione metabolism; Reductive carboxylate cycle			
let-7a	JMJD1A	Hs.531819	4				
let-7a	LOC151579	Hs.529231	4				
let-7a	LRIG3	Hs.253736	4				
let-7a	MAP4K3	Hs.468239	4	MAPK signaling pathway 04010	GO: 7254 GO: 6468 GO: 7243 GO: 6950	GO: 5524 GO: 166 GO: 4674 GO: 5083 GO: 16740	
let-7a	MESDC1	Hs.513071	4				
let-7a	MLL5	Hs.567540	4		GO: 6355	GO: 5515 GO: 8270	

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
let-7a	NDST2	Hs.225129	4	Chondroitin/Heparan sulfate biosynthesis 00532		GO: 8146 GO: 16740	GO: 5795 GO: 16021
let-7a	NID2	Hs.369840	4		GO: 7155 GO: 7160	GO: 5509 GO: 5518	GO: 5604 GO: 16020
let-7a	PBX3	Hs.428027	4		GO: 7387 GO: 9790 GO: 30902 GO: 7388 GO: 6355 GO: 45898	GO: 5515 GO: 3700	GO: 5634
let-7a	RANBP2	Hs.199561	4		GO: 46907 GO: 6457 GO: 6606	GO: 8536 GO: 5488 GO: 16853 GO: 46872 GO: 3755 GO: 8270	GO: 5643 GO: 5634
let-7a	RFXDC1	Hs.352276	4		GO: 6355 GO: 6388 GO: 6350	GO: 3677 GO: 213	GO: 214
let-7a	SEMA4C	Hs.516220	4	Axon guidance 04360	GO: 30154 GO: 7399	GO: 4872	GO: 16021 GO: 16020
let-7a	SLC20A1	Hs.187946	4				
let-7a	SLC35D2	Hs.494556	4		GO: 4	GO: 5338	GO: 8372
let-7a	SOCS1	Hs.50640	4	Insulin signaling pathway 04910; Jak-STAT signaling pathway 04630; Type II diabetes mellitus 04930	GO: 7259 GO: 7242 GO: 46426 GO: 1558 GO: 6512	GO: 5159 GO: 19901 GO: 4860	GO: 5737
let-7a	STXBP5	Hs.93534	4				
let-7a	TMEM2	Hs.494146	4				GO: 16021
let-7a	TRAPPC1	Hs.24379	4				
let-7a	TSCOT	Hs.512668	4				
let-7a	TUSC2	Hs.517981	4				
let-7a	UHRF2	Hs.493401	4				
let-7a	USP21	Hs.8015	4		GO: 6512 GO: 6511	GO: 4197 GO: 8233 GO: 5515 GO: 4221	GO: 8372
let-7a	USP32	Hs.132868	4		GO: 6512 GO: 6511	GO: 5509 GO: 4197 GO: 4221	
let-7a	ACTA1	Hs.1288	3	Smooth muscle contraction; Striated muscle contraction	GO: 7517 GO: 30240	GO: 43531 GO: 5524 GO: 3774 GO: 17022 GO: 166 GO: 5515 GO: 5200	GO: 5884 GO: 5856 GO: 1725 GO: 5865
let-7a	ACVR1B	Hs.438918	3	Adherens junction 04520; Cytokine-cytokine receptor interaction 04060; MAPK signaling pathway 04010; TGF-beta signaling pathway 04350	GO: 6468 GO: 7178	GO: 5524 GO: 287 GO: 30145 GO: 166 GO: 4674 GO: 4872 GO: 16740 GO: 5024	GO: 5887 GO: 16020
let-7a	ADAM15	Hs.312098	3		GO: 7155 GO: 7160 GO: 6508	GO: 17124 GO: 46872 GO: 4222 GO: 5515 GO: 8270	GO: 16021
let-7a	ADRB2	Hs.2551	3	Calcium signaling pathway 04020; Neuroactive ligand-receptor interaction 04080	GO: 7186 GO: 7188 GO: 187 GO: 7190 GO: 8333 GO: 7243 GO: 6898 GO: 7171)	GO: 4941 GO: 5515 GO: 4872 GO: 1584	GO: 5768 GO: 5887 GO: 5764 GO: 5886
let-7a	ANKFY1	Hs.513875	3		GO: 6897	GO: 46872 GO: 5515 GO: 8270	GO: 10008 GO: 16020

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
let-7a	ANKRD43	Hs.13308	3				
let-7a	AP1S1	Hs.489365	3		GO: 6886 GO: 6898	GO: 5515 GO: 8565	GO: 30121 GO: 5795 GO: 5802 GO: 5905
let-7a	APBB3	Hs.529449	3			GO: 5515	GO: 5737
let-7a	ARHGAP20	Hs.6136	3				
let-7a	ARL5	Hs.470233	3		GO: 6886 GO: 7264	GO: 5525 GO: 166	
let-7a	ARMC8	Hs.266826	3				
let-7a	ATXN1	Hs.434961	3			GO: 3723	GO: 5737 GO: 5634
let-7a	B3GNT6	Hs.8526	3	Blood group glycolipid biosynthesis-neolactoseries 00602; Keratan sulfate biosynthesis 00533	GO: 30311	GO: 8532 GO: 16757	GO: 5795 GO: 30173 GO: 16021
let-7a	BCL2L1	Hs.516966	3	Amyotrophic lateral sclerosis 05030; Apoptosis 04210; Jak-STAT signaling pathway 04630; Neurodegenerative Disorders 01510; Apoptosis 109581	GO: 6916 GO: 8637 GO: 8634 GO: 42981	GO: 42802	GO: 16021 GO: 16020 GO: 5741 GO: 5739
let-7a	BNC2	Hs.435309	3		GO: 6355 GO: 6350	GO: 46872 GO: 3676 GO: 8270	GO: 5634
let-7a	BRD3	Hs.522472	3		GO: 4	GO: 5554 GO: 5515	GO: 5634
let-7a	BTBD3	Hs.244590	3				
let-7a	BTG2	Hs.519162	3		GO: 6281 GO: 8285 GO: 6355 GO: 6350	GO: 3700	
let-7a	BZW2	Hs.487635	3				
let-7a	C1orf22	Hs.523811	3	Aminosugars metabolism 00530; Glycosaminoglycan degradation 00531; Nucleotide sugars metabolism 00520	GO: 5975 GO: 6487 GO: 6508	GO: 5509 GO: 16798 GO: 4571 GO: 8233	GO: 5783 GO: 16020
let-7a	CALU	Hs.7753	3		GO: 4	GO: 5509	GO: 5794 GO: 5783
let-7a	CAP1	Hs.370581	3		GO: 7190 GO: 7163 GO: 7165	GO: 3779	GO: 16020
let-7a	CASKIN1	Hs.530863	3		GO: 7165	GO: 5515	GO: 5737
let-7a	CDC34	Hs.514997	3	Ubiquitin mediated proteolysis			
let-7a	CDYL	Hs.269092	3		GO: 6333 GO: 8152 GO: 7283	GO: 3824 GO: 3682 GO: 8233	GO: 785 GO: 5634
let-7a	COIL	Hs.532795	3				GO: 5634
let-7a	COL15A1	Hs.409034	3		GO: 1525 GO: 7155 GO: 30154 GO: 6817	GO: 5515 GO: 5198	GO: 5582 GO: 5737 GO: 5578)
let-7a	COL1A1	Hs.172928	3	Cell Communication 01430; ECM-receptor interaction 04512; Focal adhesion 04510; Hemostasis 109582	GO: 8544 GO: 6817 GO: 7605 GO: 1501	GO: 5201 GO: 8147	GO: 5581 GO: 5584 GO: 5737
let-7a	COL1A2	Hs.489142	3	Cell Communication 01430; ECM-receptor interaction 04512; Focal adhesion 04510; Hemostasis 109582	GO: 4 GO: 6817 GO: 7605 GO: 1501 GO: 7169	GO: 5201 GO: 8147	GO: 5581 GO: 5584 GO: 5737
let-7a	COL24A1	Hs.47312	3				
let-7a	COL3A1	Hs.443625	3	Inflammatory Response Pathway			
let-7a	COL4A1	Hs.17441	3		GO: 6817	GO: 5201	GO: 5581 GO: 5587 GO: 5737

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
let-7a	COL4A2	Hs.508716	3				
let-7a	COL4A5	Hs.369089	3				
let-7a	CPA4	Hs.93764	3		GO: 16573 GO: 6508	GO: 4182 GO: 4180 GO: 46872 GO: 8237 GO: 8270	GO: 8372
let-7a	CPD	Hs.446079	3		GO: 6508	GO: 4182 GO: 4187 GO: 4180 GO: 46872 GO: 8472 GO: 8237 GO: 8270	GO: 16021 GO: 5624
let-7a	CPEB2	Hs.374216	3				
let-7a	CPEB3	Hs.131683	3			GO: 3676 GO: 166	
let-7a	CPEB4	Hs.127126	3				
let-7a	CPM	Hs.434948	3				
let-7a	CPSF4	Hs.489287	3	mRNA processing	GO: 6397	GO: 3723 GO: 46872 GO: 8270	GO: 5634
let-7a	CTNS	Hs.187667	3		GO: 15811 GO: 6520 GO: 6810	GO: 15184	GO: 16021 GO: 5765
let-7a	CYP46A1	Hs.25121	3		GO: 6707 GO: 6118 GO: 6629 GO: 7399 GO: 8202	GO: 20037 GO: 5506 GO: 46872 GO: 8395	GO: 5783 GO: 16021 GO: 5792
let-7a	DDEF1	Hs.106015	3		GO: 43087	GO: 5096 GO: 46872 GO: 5515 GO: 8270	GO: 16020
let-7a	DDX19	Hs.221761	3				
let-7a	DIMT1L	Hs.533222	3				
let-7a	DLC1	Hs.134296	3		GO: 7010 GO: 30308 GO: 30155 GO: 7165	GO: 5100 GO: 5515	GO: 5737 GO: 5576
let-7a	DMD	Hs.495912	3	Striated muscle contraction	GO: 4 GO: 7016 GO: 6936 GO: 7517	GO: 3779 GO: 5509 GO: 5554 GO: 5515 GO: 5200 GO: 8307 GO: 5198 GO: 8270	GO: 8372 GO: 5856 GO: 16010
let-7a	DMP1	Hs.128556	3		GO: 7155 GO: 30198 GO: 1503	GO: 5509 GO: 5178	GO: 5578)
let-7a	DMTF1	Hs.558441	3				
let-7a	DOT1L	Hs.465554	3	Lysine degradation 00310	GO: 16568	GO: 18024 GO: 8168 GO: 16740	GO: 5634
let-7a	DPF2	Hs.13495	3		GO: 6915 GO: 8624 GO: 6355 GO: 6350	GO: 46872 GO: 3676 GO: 5515 GO: 8270	GO: 5634
let-7a	DPP3	Hs.502914	3		GO: 6508	GO: 4177 GO: 17039 GO: 46872 GO: 8237 GO: 8270	GO: 5737
let-7a	DST	Hs.485616	3		GO: 30036 GO: 7155 GO: 7050 GO: 7010 GO: 7229 GO: 45104	GO: 3779 GO: 51015 GO: 5509 GO: 5178 GO: 8022 GO: 5515 GO: 5200	GO: 5604 GO: 5737 GO: 16023 GO: 5856 GO: 5615 GO: 30056 GO: 5911
let-7a	DUSP1	Hs.171695	3	; Calcium signaling pathway; Type I			

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
				diabetes mellitus;; Calcium signaling pathway			
let-7a	DUSP16	Hs.536535	3	MAPK signaling pathway 04010	GO: 45204 GO: 45209 GO: 188 GO: 6470	GO: 17017 GO: 16787	GO: 5737 GO: 5634
let-7a	DUSP9	Hs.144879	3	MAPK signaling pathway 04010	GO: 7254 GO: 188 GO: 6470	GO: 17017 GO: 16787	GO: 5737 GO: 5634
let-7a	DYRK1A	Hs.368240	3	Benzoate degradation via CoA ligation 00632; Inositol phosphate metabolism 00562; Nicotinate and nicotinamide metabolism 00760; Phosphatidylinositol signaling system 04070	GO: 7399 GO: 18108	GO: 5524 GO: 4715 GO: 166 GO: 4674 GO: 16740	GO: 5634
let-7a	EGR3	Hs.534313	3		GO: 7623 GO: 7517 GO: 6355 GO: 6350	GO: 46872 GO: 3700 GO: 8270	GO: 5634
let-7a	EIF2C1	Hs.22867	3		GO: 6412 GO: 6446	GO: 5515 GO: 3743	GO: 5850
let-7a	EIF2C3	Hs.567761	3		GO: 6412	GO: 3743	
let-7a	EIF2C4	Hs.471492	3		GO: 6412	GO: 3743	
let-7a	EPHA3	Hs.123642	3	Axon guidance 04360	GO: 6468 GO: 7165 GO: 7169	GO: 5524 GO: 5003 GO: 166 GO: 4674 GO: 4713 GO: 4872 GO: 16740	GO: 5887 GO: 16020
let-7a	EPHA4	Hs.371218	3	Calcium signaling pathway			
let-7a	ERCC6	Hs.133444	3	DNA Repair 73894	GO: 6281 GO: 6355 GO: 7605 GO: 6350 GO: 6366	GO: 5524 GO: 3677 GO: 3678 GO: 3702 GO: 4386 GO: 16787 GO: 166 GO: 5515	GO: 5634
let-7a	FARP1	Hs.567409	3		GO: 7155	GO: 8092 GO: 5085	GO: 5737 GO: 5856 GO: 16020
let-7a	FBXL19	Hs.152149	3		GO: 6508 GO: 6355 GO: 6512	GO: 3677 GO: 46872 GO: 5515 GO: 4842 GO: 8270	GO: 5737
let-7a	FGF11	Hs.528468	3				
let-7a	FLJ21986	Hs.189652	3				
let-7a	FNDC3A	Hs.508010	3	ECM-receptor interaction 04512			
let-7a	FRAS1	Hs.369448	3				
let-7a	GALNT1	Hs.514806	3	O-Glycan biosynthesis 00512	GO: 6493	GO: 5509 GO: 30145 GO: 4653 GO: 5529 GO: 16757	GO: 5795 GO: 16021
let-7a	GATM	Hs.75335	3	Urea cycle and metabolism of amino groups; Glycine, serine and threonine metabolism; Arginine and proline metabolism			
let-7a	GGA3	Hs.87726	3		GO: 6886 GO: 6461	GO: 30306 GO: 5515 GO: 8565	GO: 5795 GO: 5802 GO: 30130 GO: 16020

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
let-7a	GNAL	Hs.136295	3	Calcium signaling pathway 04020	GO: 7186 GO: 7165	GO: 5525 GO: 3924 GO: 166 GO: 4871	
let-7a	GNG5	Hs.554749	3	Energy Metabolism 163685	GO: 7186 GO: 7165	GO: 4871	GO: 5834
let-7a	GNPTAB	Hs.46850	3				
let-7a	GRIK2	Hs.98262	3	Neuroactive ligand-receptor interaction 04080	GO: 7215 GO: 6811 GO: 6813 GO: 7268 GO: 6810	GO: 5234 GO: 5216 GO: 4970 GO: 15277 GO: 5267 GO: 4872 GO: 5215	GO: 5887 GO: 16020 GO: 45211
let-7a	HAND1	Hs.152531	3		GO: 7275 GO: 7507 GO: 6355 GO: 6366	GO: 3700	GO: 5634
let-7a	HAS2	Hs.159226	3			GO: 50501 GO: 16757	GO: 5887
let-7a	HDHD1A	Hs.185910	3		GO: 4 GO: 8152	GO: 3824 GO: 5554	GO: 8372
let-7a	HECTD2	Hs.535293	3		GO: 15671 GO: 6512	GO: 20037 GO: 5344 GO: 4842	GO: 5622
let-7a	HIC2	Hs.517434	3		GO: 45892 GO: 6350	GO: 3677 GO: 46872 GO: 8022 GO: 8270	GO: 5634
let-7a	HOMER2	Hs.459142	3		GO: 7216		
let-7a	HOXA9	Hs.127428	3		GO: 4 GO: 7275 GO: 6355	GO: 5554 GO: 3700 GO: 16563	GO: 5634
let-7a	HOXB4	Hs.532669	3		GO: 7275 GO: 6355	GO: 3700	GO: 5634
let-7a	HOXD1	Hs.83465	3		GO: 7275 GO: 6355	GO: 3700	GO: 5634
let-7a	HTR4	Hs.483773	3	Calcium signaling pathway 04020; Neuroactive ligand-receptor interaction 04080	GO: 7187 GO: 7165	GO: 4935 GO: 4872 GO: 1584 GO: 4993	GO: 5887
let-7a	IL13	Hs.845	3	Cytokine-cytokine receptor interaction 04060; Jak-STAT signaling pathway 04630	GO: 19735) GO: 6928 GO: 8283 GO: 7267 GO: 6954 GO: 7165	GO: 8009 GO: 5144 GO: 4871	GO: 5615 GO: 5625
let-7a	INPP5A	Hs.523360	3	Inositol phosphate metabolism 00562; Phosphatidylinositol signaling system 04070	GO: 7154	GO: 16787 GO: 4437 GO: 4445	GO: 16020
let-7a	IRS2	Hs.442344	3	Adipocytokine signaling pathway 04920; Insulin signaling pathway 04910; Type II diabetes mellitus 04930; Insulin receptor mediated signalling 74752	GO: 6006 GO: 8284 GO: 7165	GO: 5158 GO: 4871	
let-7a	ITGB3	Hs.218040	3	ECM-receptor interaction 04512; Focal adhesion 04510; Hematopoietic cell lineage 04640; Regulation of actin cytoskeleton 04810; Hemostasis 109582	GO: 7596 GO: 7155 GO: 7160 GO: 7275 GO: 7229	GO: 42802 GO: 4872	GO: 8305
let-7a	KCNC2	Hs.27214	3				
let-7a	KIF1B	Hs.97858	3		GO: 8089 GO: 9790 GO: 7018 GO: 7270 GO: 7274	GO: 5524 GO: 16887 GO: 19894 GO: 8017 GO: 3777	GO: 30659 GO: 5874 GO: 5875 GO: 5739

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
let-7a	KIF2	Hs.558351	3		GO: 7018	GO: 166 GO: 5515 GO: 5524 GO: 3777	GO: 5856 GO: 5874
let-7a	KLF9	Hs.150557	3	Circadian Exercise	GO: 6357 GO: 6350	GO: 166 GO: 46872 GO: 3700 GO: 8270	GO: 5875 GO: 5634
let-7a	KPNA4	Hs.288193	3		GO: 6607 GO: 6886	GO: 5488 GO: 8565	GO: 5634
let-7a	LOC283859	Hs.298434	3	Wnt signaling pathway 04310			
let-7a	LOC643176	Hs.403917	3				
let-7a	LOXL3	Hs.469045	3				
let-7a	LOXL4	Hs.306814	3	Arginine and proline metabolism 00330		GO: 5507 GO: 46872 GO: 16491 GO: 4720 GO: 5044	GO: 16020
let-7a	LRIG1	Hs.518055	3				
let-7a	LRIG2	Hs.448972	3				
let-7a	MAP3K7IP2	Hs.269775	3	MAPK signaling pathway 04010; Toll-like receptor signaling pathway 04620			
let-7a	MED6	Hs.497353	3	MED6	GO: 45944	GO: 3702 GO: 4872 GO: 3713	GO: 119 GO: 5634
let-7a	MEF2D	Hs.314327	3		GO: 7517 GO: 6355 GO: 6350 GO: 6366	GO: 3713 GO: 3700	GO: 5634
let-7a	MEIS2	Hs.510989	3		GO: 122 GO: 6355	GO: 3704 GO: 3714 GO: 3700	GO: 5634
let-7a	MGAT4A	Hs.177576	3	N-Glycan biosynthesis			
let-7a	MTPN	Hs.43297	3				
let-7a	MYCN	Hs.25960	3		GO: 6357	GO: 5515 GO: 3700	GO: 785 GO: 5634
let-7a	NAB1	Hs.107474	3		GO: 16481 GO: 6355 GO: 6350	GO: 3676 GO: 16564	GO: 5634
let-7a	NCOA3	Hs.382168	3		GO: 30521 GO: 45893 GO: 7165	GO: 8415 GO: 50681 GO: 4402 GO: 5515 GO: 4871 GO: 46966 GO: 3713 GO: 30528 GO: 16740	GO: 5634
let-7a	NLK	Hs.208759	3	Adherens junction 04520; MAPK signaling pathway 04010; Wnt signaling pathway 04310	GO: 30178 GO: 6468 GO: 7243 GO: 6355	GO: 5524 GO: 4707 GO: 287 GO: 166 GO: 5515 GO: 4674 GO: 4713 GO: 16740	GO: 5634
let-7a	NME4	Hs.9235	3				
let-7a	NPHP3	Hs.511991	3				
let-7a	NUMBL	Hs.326953	3	Notch signaling pathway 04330	GO: 7399		
let-7a	NUP98	Hs.524750	3		GO: 6260 GO: 6999 GO: 6913 GO: 59 GO: 15031	GO: 5515 GO: 17056 GO: 5215	GO: 5643 GO: 5654
let-7a	OPRM1	Hs.2353	3	Neuroactive ligand-receptor interaction 04080	GO: 7186 GO: 7187 GO: 7610 GO: 8285 GO: 7600 GO: 7165	GO: 4988 GO: 4872 GO: 1584	GO: 5794 GO: 5783 GO: 16021 GO: 5887 GO: 5886

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
let-7a	P4HA2	Hs.519568	3	Arginine and proline metabolism 00330	GO: 19538	GO: 31418 GO: 5489 GO: 5506 GO: 46872 GO: 16491 GO: 16706 GO: 16702 GO: 4656 GO: 5515	GO: 5783
let-7a	PAK1	Hs.435714	3	Axon guidance 04360; Focal adhesion 04510; MAPK signaling pathway 04010; Natural killer cell mediated cytotoxicity 04650; Regulation of actin cytoskeleton 04810; T cell receptor signaling pathway 04660	GO: 7254 GO: 6915 GO: 6468	GO: 5524 GO: 166 GO: 5515 GO: 4674 GO: 4713 GO: 16740	
let-7a	PANX2	Hs.440092	3				GO: 5921 GO: 16021
let-7a	PAPPA	Hs.494928	3		GO: 30154 GO: 7565 GO: 6508	GO: 46872 GO: 8237 GO: 8270	GO: 5615 GO: 16020
let-7a	PAX3	Hs.42146	3		GO: 6915 GO: 7275 GO: 7399 GO: 9887 GO: 6355 GO: 7605 GO: 6366	GO: 3700	GO: 5634
let-7a	PBX2	Hs.509545	3		GO: 7387 GO: 7388 GO: 6355	GO: 5515 GO: 3700	GO: 5634
let-7a	PDGFB	Hs.1976	3	Cytokine-cytokine receptor interaction 04060; Focal adhesion 04510; Gap junction 04540; MAPK signaling pathway 04010; Regulation of actin cytoskeleton 04810; Hemostasis 109582	GO: 8283 GO: 74 GO: 9611	GO: 8083 GO: 5161	GO: 5576 GO: 16020
let-7a	PHF8	Hs.133352	3		GO: 6355	GO: 46872 GO: 5515 GO: 8270	
let-7a	PLAGL2	Hs.154104	3		GO: 6355 GO: 6350	GO: 46872 GO: 3700 GO: 8270	GO: 5634
let-7a	PLCB4	Hs.472101	3	Calcium signaling pathway 04020; Gap junction 04540; Inositol phosphate metabolism 00562; Phosphatidylinositol signaling system 04070; Wnt signaling pathway 04310	GO: 7242 GO: 16042 GO: 6629	GO: 5509 GO: 16787 GO: 4435 GO: 4871	
let-7a	PLD3	Hs.257008	3		GO: 8152	GO: 3824 GO: 5085	
let-7a	PLEKHG6	Hs.163953	3				
let-7a	PLEKHO1	Hs.438824	3				
let-7a	PLGLB2	Hs.528525	3				
let-7a	POGZ	Hs.489873	3		GO: 7275	GO: 3677 GO: 46872 GO: 3676 GO: 8270	GO: 5634
let-7a	POLH	Hs.439153	3				
let-7a	PPARGC1A	Hs.527078	3	Adipocytokine signaling pathway 04920; Insulin signaling pathway 04910	GO: 8380 GO: 30521 GO: 50873 GO: 1678 GO: 45333 GO: 7586	GO: 3677 GO: 3723 GO: 16455 GO: 50681 GO: 30374 GO: 166	GO: 5665 GO: 5634

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
					GO: 19395 GO: 6094 GO: 6397 GO: 7005 GO: 46321 GO: 45722 GO: 35066 GO: 45893 GO: 6461 GO: 50821 GO: 42594 GO: 1659 GO: 6350 GO: 6367	GO: 8134	
let-7a	PPP3CA	Hs.435512	3	Amyotrophic lateral sclerosis 05030; Apoptosis 04210; Axon guidance 04360; B cell receptor signaling pathway 04662; Calcium signaling pathway 04020; MAPK signaling pathway 04010; Natural killer cell mediated cytotoxicity 04650; T cell receptor signaling pathway 04660; Wnt signaling pathway 04310	GO: 6470	GO: 5509 GO: 5516 GO: 16787 GO: 5506 GO: 4722 GO: 8270	GO: 5955 GO: 5634
let-7a	PRDM2	Hs.371823	3		GO: 6355	GO: 46872 GO: 3676 GO: 3700 GO: 8270	GO: 5634
let-7a	PRRX1	Hs.283416	3				
let-7a	PTPRU	Hs.19718	3		GO: 7155 GO: 6470 GO: 7185	GO: 16787 GO: 4725 GO: 4872 GO: 5001	GO: 5887 GO: 16020
let-7a	PYGO2	Hs.433795	3				
let-7a	QARS	Hs.79322	3	Aminoacyl-tRNA synthetases 00970; Glutamate metabolism 00251	GO: 6425 GO: 6424 GO: 6412	GO: 5524 GO: 4818 GO: 4819 GO: 16874 GO: 166 GO: 5515	GO: 5737 GO: 5625
let-7a	RAI16	Hs.491223	3				
let-7a	RAPGEF6	Hs.483329	3				
let-7a	RASL10B	Hs.437035	3				
let-7a	RB1	Hs.408528	3	Cell cycle 04110; Cell Cycle 69278	GO: 30521 GO: 75 GO: 45786 GO: 6469 GO: 122 GO: 45893 GO: 6355 GO: 6350	GO: 50681 GO: 5554 GO: 5515 GO: 3713 GO: 3700	GO: 785 GO: 5634
let-7a	RBM9	Hs.282998	3	Ribosomal Proteins			
let-7a	RDH10	Hs.244940	3				
let-7a	RDX	Hs.263671	3	Regulation of actin cytoskeleton 04810	GO: 51016 GO: 7016	GO: 3779 GO: 5488 GO: 5198	GO: 15629 GO: 5737 GO: 5886
let-7a	RGAG1	Hs.201071	3				
let-7a	RNF20	Hs.168095	3		GO: 16567	GO: 46872 GO: 4842 GO: 8270	GO: 151
let-7a	RNF38	Hs.333503	3		GO: 16567	GO: 46872 GO: 4842 GO: 8270	GO: 151
let-7a	RNF44	Hs.434888	3		GO: 16567	GO: 46872 GO: 4842 GO: 8270	GO: 151

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
let-7a	RNF5	Hs.534342	3		GO: 16567	GO: 46872 GO: 5515 GO: 4842 GO: 8270	GO: 151
let-7a	RUFY3	Hs.7972	3				
let-7a	SCN5A	Hs.556087	3		GO: 6812 GO: 6936 GO: 8016 GO: 6814	GO: 5261 GO: 31402 GO: 5248	GO: 16021 GO: 16020 GO: 5624 GO: 1518
let-7a	SCUBE3	Hs.12923	3				
let-7a	SEC24C	Hs.81964	3		GO: 6888 GO: 6886	GO: 3779 GO: 5554 GO: 5515	GO: 30127 GO: 5795 GO: 5783
let-7a	SEMA3F	Hs.32981	3	Axon guidance 04360	GO: 7275		GO: 5615
let-7a	SEMA4G	Hs.567556	3	Axon guidance 04360	GO: 30154 GO: 7399	GO: 4872	GO: 16021 GO: 16020
let-7a	SENP2	Hs.401388	3	Wnt signaling pathway 04310	GO: 6508 GO: 30111 GO: 6512	GO: 16929 GO: 8234 GO: 5515	GO: 5643 GO: 5634
let-7a	SENP5	Hs.533124	3				
let-7a	SFRS12	Hs.519347	3	mRNA processing			
let-7a	SLC25A18	Hs.282982	3		GO: 6810	GO: 5488 GO: 15293	GO: 16021 GO: 5743 GO: 5739
let-7a	SLC25A18	Hs.570482	3		GO: 6810	GO: 5488 GO: 15293	GO: 16021 GO: 5743 GO: 5739
let-7a	SLC25A4	Hs.246506	3	Calcium signaling pathway 04020; Nucleotide metabolism 15869	GO: 6091 GO: 2 GO: 6839 GO: 6810	GO: 15207 GO: 5488 GO: 5215	GO: 16021 GO: 5887 GO: 16020 GO: 5743 GO: 5739
let-7a	SLC4A4	Hs.5462	3		GO: 6820 GO: 6810	GO: 5452 GO: 8510	GO: 16021 GO: 5887 GO: 16020
let-7a	SLC6A1	Hs.443874	3				
let-7a	SLC6A15	Hs.44424	3		GO: 6836	GO: 5328 GO: 15293	GO: 5887 GO: 16020
let-7a	SLCO5A1	Hs.443609	3		GO: 6810	GO: 5215	GO: 16021 GO: 16020
let-7a	SMARCAD1	Hs.410406	3				
let-7a	SMARCC1	Hs.476179	3		GO: 6333 GO: 6338 GO: 45893 GO: 45449 GO: 6357	GO: 3677 GO: 3682 GO: 5515 GO: 3713	GO: 16514 GO: 785 GO: 5654 GO: 5634
let-7a	SPATA2	Hs.48513	3		GO: 30154 GO: 7283	GO: 5554	GO: 5737
let-7a	STARD13	Hs.507704	3				
let-7a	STRBP	Hs.287659	3				
let-7a	SYT1	Hs.310545	3				
let-7a	TAF5	Hs.96103	3	RNA transcription			
let-7a	TARBP2	Hs.326	3		GO: 6469 GO: 45946 GO: 45070 GO: 6357 GO: 46782	GO: 3725 GO: 46982	GO: 5622 GO: 5634
let-7a	TBX5	Hs.381715	3		GO: 7507 GO: 9653 GO: 45893 GO: 6355 GO: 6350	GO: 3702 GO: 5515 GO: 3700	GO: 5634
let-7a	TGFBR1	Hs.494622	3	Adherens junction 04520; Cytokine-cytokine receptor interaction 04060; MAPK signaling pathway 04010; TGF-beta signaling pathway 04350	GO: 6468 GO: 7165 GO: 7181 GO: 7178	GO: 5524 GO: 287 GO: 30145 GO: 166 GO: 4713 GO: 4872 GO: 16740 GO: 5024 GO: 5025	GO: 16021 GO: 5887 GO: 16020

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
let-7a	TIMM17B	Hs.30570	3		GO: 6626	GO: 15450	GO: 16021 GO: 5744 GO: 5739
let-7a	Transcribed locus	Hs.408973	3				
let-7a	Transcribed locus	Hs.560163	3				
let-7a	TRIB2	Hs.467751	3		GO: 6468 GO: 43405	GO: 5524 GO: 166 GO: 4674 GO: 4713 GO: 16740	GO: 5737
let-7a	TRIM41	Hs.441488	3				
let-7a	TSC22D2	Hs.52526	3		GO: 6355	GO: 3700	
let-7a	TTLL4	Hs.471405	3		GO: 6464	GO: 16874 GO: 4835	
let-7a	ULK2	Hs.168762	3		GO: 6468	GO: 5524 GO: 166 GO: 4674 GO: 4713 GO: 16740	
let-7a	USP25	Hs.473370	3		GO: 6508 GO: 6512 GO: 6511	GO: 4197 GO: 4221	
let-7a	VAV3	Hs.267659	3	B cell receptor signaling pathway 04662; Focal adhesion 04510; Natural killer cell mediated cytotoxicity 04650; Regulation of actin cytoskeleton 04810	GO: 7242 GO: 7264	GO: 5096 GO: 5070 GO: 19992 GO: 5085 GO: 46872 GO: 8270	
let-7a	VSNL1	Hs.444212	3			GO: 5509	
let-7a	WDFY3	Hs.480116	3				
let-7a	WNT1	Hs.248164	3	Hedgehog signaling pathway 04340; Wnt signaling pathway 04310	GO: 30154 GO: 1708 GO: 16477 GO: 7417 GO: 7163 GO: 7223 GO: 9653 GO: 7283	GO: 5102	GO: 5576 GO: 5625
let-7a	XKR8	Hs.55024	3				GO: 16021
let-7a	ZC3H3	Hs.521915	3			GO: 46872 GO: 3676 GO: 8270	
let-7a	ZCCHC5	Hs.134873	3			GO: 46872 GO: 3676 GO: 8270	
let-7a	ZFYVE26	Hs.98041	3			GO: 3676 GO: 8270	GO: 5634
let-7a	ZNF318	Hs.509718	3			GO: 3824 GO: 3676 GO: 3735 GO: 8270	GO: 5634
let-7a	ZNF644	Hs.173001	3		GO: 6355 GO: 6350	GO: 3677 GO: 46872 GO: 8270	GO: 5634
let-7a	ZZZ3	Hs.480506	3		GO: 45449	GO: 3677 GO: 8270	GO: 5634
miR-182*	DOCK9	Hs.314413	4				
miR-182*	AARS	Hs.315137	3	Alanine and aspartate metabolism 00252; Aminoacyl-tRNA synthetases 00970	GO: 6419 GO: 6412 GO: 8033	GO: 5524 GO: 4813 GO: 16874 GO: 3676 GO: 166 GO: 49	GO: 5737 GO: 5625
miR-182*	ABCG1	Hs.124649	3	ABC transporters - General 02010	GO: 42632 GO: 8203 GO: 9720 GO: 6869 GO: 10033	GO: 5524 GO: 16887 GO: 42626 GO: 15196 GO: 166 GO: 15646 GO: 46983 GO: 15216	GO: 5795 GO: 5783 GO: 5887 GO: 16020 GO: 5624

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
miR-182*	ALDH18A1	Hs.500645	3	Urea cycle and metabolism of amino groups 00220	GO: 8652 GO: 8152 GO: 6561	GO: 3942 GO: 4349 GO: 4350 GO: 16301 GO: 16491 GO: 16740	GO: 5739 GO: 19866
miR-182*	BACH2	Hs.269764	3		GO: 6355 GO: 6350	GO: 3677 GO: 5515	GO: 5634
miR-182*	CBX3	Hs.381189	3	Circadian Exercise	GO: 6333 GO: 16568 GO: 6355 GO: 6350	GO: 3682 GO: 5515	GO: 785 GO: 5634
miR-182*	CD36	Hs.120949	3	Adipocytokine signaling pathway 04920; ECM-receptor interaction 04512; Hematopoietic cell lineage 04640; Hemostasis 109582	GO: 7596 GO: 7155 GO: 6631 GO: 6629 GO: 6810	GO: 5515 GO: 4872	GO: 5887 GO: 16020 GO: 5624
miR-182*	CRLF1	Hs.114948	3		GO: 19735 + F280	GO: 19955 GO: 4872	GO: 5615
miR-182*	CXXC5	Hs.189119	3			GO: 3677 GO: 8270	
miR-182*	FAT	Hs.481371	3		GO: 7155 GO: 7267 GO: 7156 GO: 9653	GO: 5509 GO: 5515	GO: 5887 GO: 16020
miR-182*	FBXW11	Hs.484138	3	Hedgehog signaling pathway 04340; Ubiquitin mediated proteolysis 04120; Wnt signaling pathway 04310	GO: 16055 GO: 16567	GO: 4842	GO: 151
miR-182*	FYCO1	Hs.200227	3				
miR-182*	KCMF1	Hs.345694	3				
miR-182*	GALNT1	Hs.514806	3	O-Glycan biosynthesis 00512	GO: 6493	GO: 5509 GO: 30145 GO: 4653 GO: 5529 GO: 16757	GO: 5795 GO: 16021
miR-182*	HDAC7A	Hs.200063	3	Cell cycle 04110	GO: 30183 GO: 16568 GO: 6954 GO: 45843 GO: 7399 GO: 74 GO: 6355 GO: 6350	GO: 4407 GO: 16787 GO: 16566 GO: 8134	GO: 5737 GO: 118 GO: 5634
miR-182*	HDHD2	Hs.465041	3				
miR-182*	HOXB4	Hs.532669	3		GO: 7275 GO: 6355	GO: 3700	GO: 5634
miR-182*	HRMT1L4	Hs.504530	3	Aminophosphonate metabolism 00440; Androgen and estrogen metabolism 00150; Histidine metabolism 00340; Nitrobenzene degradation 00626; Selenoamino acid metabolism 00450; Tryptophan metabolism 00380; Tyrosine metabolism 00350		GO: 8757 GO: 16740	GO: 5634
miR-182*	ITGA10	Hs.158237	3	ECM-receptor interaction 04512; Focal adhesion 04510; Regulation of actin cytoskeleton 04810	GO: 7155 GO: 7160 GO: 7229	GO: 5509 GO: 5518 GO: 287 GO: 4872	GO: 16021 GO: 8305
miR-182*	LGI1	Hs.533670	3		GO: 8283 GO: 7399		
miR-182*	MAPK9	Hs.484371	3	Adipocytokine signaling pathway 04920; Focal adhesion 04510; Insulin signaling pathway 04910; MAPK signaling pathway 04010; Toll-like	GO: 7254 GO: 6468 GO: 6950	GO: 5524 GO: 4705 GO: 4707 GO: 166 GO: 5515 GO: 4674	

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
				receptor signaling pathway 04620; Type II diabetes mellitus 04930; Wnt signaling pathway 04310		GO: 4713 GO: 16740	
miR-182*	PLA2G6	Hs.170479	3	Glycerophospholipid metabolism 00564; MAPK signaling pathway 04010; Prostaglandin and leukotriene metabolism 00590	GO: 16042 GO: 6644	GO: 16787 GO: 4623	GO: 5737 GO: 16020
miR-182*	PLAGL2	Hs.154104	3		GO: 6355 GO: 6350	GO: 46872 GO: 3700 GO: 8270	GO: 5634
miR-182*	PLCL2	Hs.202010	3				
miR-182*	RAB5A	Hs.475663	3		GO: 6897 GO: 6886 GO: 7264	GO: 5525 GO: 3924 GO: 166 GO: 5515	GO: 5769
miR-182*	RAB6A	Hs.503222	3		GO: 6888 GO: 15031 GO: 7264	GO: 5525 GO: 3924 GO: 166 GO: 5515	GO: 5795
miR-182*	RBM12	Hs.246413	3				
miR-182*	RPS6KA1	Hs.149957	3	Ribosomal Proteins;; Calcium signaling pathway; Phosphatidylinositol signaling system	GO: 6468 GO: 7165	GO: 5524 GO: 166 GO: 4672 GO: 4674 GO: 4713 GO: 3735 GO: 16740	
miR-182*	SBF1	Hs.449098	3		GO: 46839 GO: 6470	GO: 4437 GO: 8138	GO: 16021 GO: 5634
miR-182*	SLC18A1	Hs.158322	3		GO: 15893 GO: 15844	GO: 15238 GO: 8504 GO: 15293	GO: 16021 GO: 5624
miR-182*	SMAD7	Hs.465087	3	TGF-beta signaling pathway 04350	GO: 6355 GO: 6950 GO: 6350 GO: 7179	GO: 5515 GO: 5076 GO: 30617	GO: 5634
miR-182*	TACR3	Hs.942	3	Calcium signaling pathway 04020; Neuroactive ligand-receptor interaction 04080	GO: 7165 GO: 7217	GO: 4872 GO: 1584 GO: 4995	GO: 5887 GO: 5886
miR-182*	TCERG1	Hs.443465	3		GO: 6355 GO: 6350 GO: 6366	GO: 3702 GO: 5515 GO: 3713	GO: 5634
miR-182*	TFIP11	Hs.20225	3		GO: 30154 GO: 30198 GO: 1503 GO: 45045	GO: 3676 GO: 5515	GO: 5634
miR-182*	TP53INP2	Hs.516994	3				
miR-182*	UBE2B	Hs.385986	3	Ubiquitin mediated proteolysis;	GO: 6281 GO: 6512	GO: 16874 GO: 8642 GO: 4842	GO: 16020 GO: 5634
miR-182*	VAT1	Hs.514199	3		GO: 16049	GO: 3677 GO: 16491 GO: 8270	GO: 16021 GO: 5634 GO: 8021
miR-182*	ZFP36L2	Hs.503093	3		GO: 8283	GO: 46872 GO: 3676 GO: 3700 GO: 8270	GO: 5634
miR-182*	ZIC3	Hs.111227	3		GO: 7368 GO: 6355 GO: 6350	GO: 3677 GO: 46872 GO: 8270	GO: 5634
miR-372	ATXN1	Hs.434961	4			GO: 3723	GO: 5737 GO: 5634
miR-372	POLH	Hs.439153	4				
miR-372	BCL11B	Hs.510396	4		GO: 6355 GO: 6350	GO: 46872 GO: 3676 GO: 8270	GO: 5634

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
miR-372	DPYSL5	Hs.299315	4	Axon guidance 04360	GO: 7411 GO: 7399 GO: 7165	GO: 16787	
miR-372	INHBB	Hs.1735	4	Cytokine-cytokine receptor interaction 04060; TGF-beta signaling pathway 04350	GO: 30154 GO: 6952 GO: 40007 GO: 46882 GO: 48178 GO: 1541	GO: 5125 GO: 8083 GO: 5179 GO: 46789 GO: 42803	GO: 5576
miR-372	MAP3K11	Hs.502872	4	; Calcium signaling pathway	GO: 80 GO: 7257 GO: 8283 GO: 7017 GO: 46777 GO: 51259	GO: 5524 GO: 4706 GO: 166 GO: 5515 GO: 42803 GO: 4674 GO: 4713	GO: 5813 GO: 5874
miR-372	MYCN	Hs.25960	4		GO: 6357	GO: 5515 GO: 3700	GO: 785 GO: 5634
miR-372	NEUROD6	Hs.45152	4		GO: 6355	GO: 3677 GO: 30528	GO: 5634
miR-372	NFIB	Hs.370359	4		GO: 6260 GO: 6355 GO: 6350	GO: 3700	GO: 5634
miR-372	PARP8	Hs.369581	4				
miR-372	CDNA FLJ38785 fis	Hs.406990	4				
miR-372	RBBP7	Hs.495755	4		GO: 8283 GO: 7275	GO: 5515	GO: 5634
miR-372	SS18L1	Hs.154429	4			GO: 5515	
miR-372	TLE4	Hs.444213	4		GO: 4 GO: 7222 GO: 6355	GO: 5554	GO: 5634
miR-372	ADAM9	Hs.2442	3		GO: 7243 GO: 6508	GO: 17124 GO: 5178 GO: 46872 GO: 4222 GO: 5515 GO: 19901 GO: 8270	GO: 5887
miR-372	AEBP2	Hs.126497	3				
miR-372	AMPD2	Hs.82927	3	Purine metabolism			
miR-372	ANK2	Hs.567235	3	Ribosomal Proteins			
miR-372	APBB2	Hs.479602	3		GO: 30048 GO: 7409 GO: 7050 GO: 7242 GO: 45749 GO: 30308 GO: 50821	GO: 1540 GO: 35035 GO: 8134	GO: 30426 GO: 30027 GO: 16020 GO: 5634 GO: 45202
miR-372	APP	Hs.434980	3	Alzheimer's disease 05010; Neurodegenerative Disorders 01510; Hemostasis 109582	GO: 7219 GO: 6915 GO: 7155 GO: 6878 GO: 6897 GO: 50905	GO: 5507 GO: 8201 GO: 5506 GO: 46872 GO: 5515 GO: 4867 GO: 8270 GO: 5096	GO: 9986 GO: 5905 GO: 5576 GO: 5887
miR-372	ARHGAP9	Hs.437126	3				
miR-372	ARHGEF10	Hs.98594	3				
miR-372	ARID4A	Hs.161000	3		GO: 6333 GO: 45892 GO: 6350 GO: 6366	GO: 3682 GO: 5515 GO: 3700 GO: 16564	GO: 785 GO: 5634 GO: 17053
miR-372	ARID4B	Hs.533633	3			GO: 3677 GO: 3676	GO: 5622
miR-372	ATP2B2	Hs.268942	3	Calcium signaling pathway 04020	GO: 6816 GO: 6812 GO: 8152	GO: 5524 GO: 5509 GO: 5388 GO: 5516 GO: 16787 GO: 16820	GO: 16021 GO: 5886
miR-372	ATP2B4	Hs.343522	3	Calcium signaling pathway 04020	GO: 6816 GO: 6812 GO: 8152	GO: 5524 GO: 5509 GO: 5388	GO: 5887 GO: 5886

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
						GO: 5516 GO: 16787 GO: 16820	
miR-372	BAHD1	Hs.22109	3				
miR-372	BCL11A	Hs.370549	3		GO: 30097 GO: 6355 GO: 6350	GO: 46872 GO: 3676 GO: 8270 GO: 5554	GO: 5737 GO: 5634
miR-372	BRP44L	Hs.172755	3				
miR-372	BTG1	Hs.255935	3	Circadian Exercise	GO: 16477 GO: 30308 GO: 8285 GO: 45766 GO: 45603 GO: 43085	GO: 19900 GO: 3712	GO: 5737 GO: 5634
miR-372	C15orf17	Hs.367690	3				
miR-372	C16orf28	Hs643536	3		GO: 16567	GO: 4842 GO: 8270	GO: 151
miR-372	CCND2	Hs.376071	3	Cell cycle 04110; Focal adhesion 04510; Jak-STAT signaling pathway 04630; Wnt signaling pathway 04310; Cell Cycle 69278	GO: 51301 GO: 74		GO: 5634
miR-372	CDC2L6	Hs.159118	3				
miR-372	CFL2	Hs.180141	3	G13 Signaling Pathway			
miR-372	COL23A1	Hs.413494	3				
miR-372	TNXB	Hs.42853	3	G1 to S cell cycle; Smooth muscle contraction			
miR-372	CRIM1	Hs.332847	3				
miR-372	CUL4A	Hs.339735	3				
miR-372	DAZAP2	Hs.369761	3	Circadian Exercise			
miR-372	DMTF1	Hs.558441	3				
miR-372	E2F5	Hs.445758	3	Cell cycle 04110; TGF-beta signaling pathway 04350; Cell Cycle 69278	GO: 74 GO: 6355 GO: 6350	GO: 5515 GO: 3700	GO: 5634 GO: 5667
miR-372	EIF2C1	Hs.22867	3		GO: 6412 GO: 6446	GO: 5515 GO: 3743	GO: 5850
miR-372	EPAS1	Hs.468410	3		GO: 1525 GO: 30154 GO: 6355 GO: 1666 GO: 7165 GO: 6366	GO: 3705 GO: 35035 GO: 5515 GO: 4871 GO: 3713	GO: 5634
miR-372	EPHA2	Hs.171596	3	Axon guidance 04360	GO: 7275 GO: 6468 GO: 7165 GO: 7169	GO: 5524 GO: 5003 GO: 166 GO: 4674 GO: 4872 GO: 16740	GO: 5887 GO: 16020
miR-372	ERBB4	Hs.390729	3	Calcium signaling pathway 04020; Dorso-ventral axis formation 04320	GO: 8283 GO: 7275 GO: 6468 GO: 7169	GO: 5524 GO: 5006 GO: 166 GO: 5515 GO: 4872 GO: 16740	GO: 5887 GO: 16020
miR-372	FBXL11	Hs.124147	3		GO: 6355 GO: 6512	GO: 3677 GO: 46872 GO: 5515 GO: 8270	
miR-372	Transcribed locus	Hs.246781	3				
miR-372	FNDC3A	Hs.508010	3	ECM-receptor interaction 04512			
miR-372	GCAT	Hs.54609	3	Glycine, serine and threonine metabolism 00260	GO: 6520 GO: 9058	GO: 8415 GO: 8890 GO: 16874 GO: 16769	GO: 5739
miR-372	GPR161	Hs.271809	3	GPCRDB Class A Rhodopsin-like2			

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
miR-372	GPR6	Hs.46332	3	GPCRDB Class A Rhodopsin-like	GO: 7186 GO: 7165	GO: 16526 GO: 4872 GO: 1584	GO: 5887
miR-372	HBP1	Hs.162032	3		GO: 16055 GO: 6355 GO: 6350	GO: 3677	GO: 5634
miR-372	HIC2	Hs.517434	3		GO: 45892 GO: 6350	GO: 3677 GO: 46872 GO: 8022 GO: 8270	GO: 5634
miR-372	HNRPH3	Hs.198158	3				
miR-372	IRF2	Hs.374097	3	Apoptosis	GO: 8283 GO: 6955 GO: 122 GO: 6355 GO: 6350	GO: 3702 GO: 3700	GO: 5634
miR-372	KCNMA1	Hs.568865	3				
miR-372	KIF3B	Hs.369670	3				
miR-372	KLF12	Hs.373857	3		GO: 6357 GO: 6350	GO: 46872 GO: 3714 GO: 3700 GO: 8270	GO: 5634
miR-372	LATS2	Hs.78960	3		GO: 82 GO: 7049 GO: 51301 GO: 9755 GO: 7067 GO: 45736 GO: 6468	GO: 5524 GO: 287 GO: 166 GO: 4674 GO: 4713 GO: 16740	GO: 5634 GO: 922
miR-372	LOC641518	Hs.535760	3	TGF Beta Signaling Pathway			
miR-372	LEF1	Hs.555947	3	Adherens junction 04520; Wnt signaling pathway 04310	GO: 16055 GO: 6355 GO: 6350	GO: 3677	GO: 5634
miR-372	LHX6	Hs.103137	3		GO: 7420 GO: 6355	GO: 46872 GO: 3700 GO: 8270	GO: 5634
miR-372	LUC7L2	Hs.530118	3			GO: 46872 GO: 8270	
miR-372	MBNL2	Hs.125715	3				
miR-372	MEF2C	Hs.444409	3	MAPK signaling pathway 04010	GO: 7517 GO: 7399 GO: 6355 GO: 6350 GO: 6366	GO: 3702 GO: 3713 GO: 3700	GO: 5634
miR-372	MKRN1	Hs.490347	3		GO: 4 GO: 16567	GO: 46872 GO: 5554 GO: 3676 GO: 5515 GO: 4842 GO: 8270	GO: 8372 GO: 151
miR-372	MTMR3	Hs.474536	3		GO: 46839 GO: 6470	GO: 16787 GO: 4437 GO: 46872 GO: 4722 GO: 4725 GO: 8270	GO: 5737 GO: 5624
miR-372	NEK9	Hs.7200	3		GO: 7049 GO: 51301 GO: 7067 GO: 6468	GO: 5524 GO: 287 GO: 166 GO: 4674 GO: 16740	
miR-372	NEUROD1	Hs.72981	3		GO: 30154 GO: 7399 GO: 6355	GO: 3677 GO: 3702	GO: 5634
miR-372	NPAS3	Hs.509113	3		GO: 6355 GO: 7165	GO: 3677 GO: 4871 GO: 30528	GO: 5634
miR-372	NR4A2	Hs.165258	3	Nuclear Receptors	GO: 19735) GO: 6355 GO: 7165 GO: 6350	GO: 4879 GO: 46872 GO: 3707 GO: 3700 GO: 8270	GO: 5634
miR-372	NR4A3	Hs.279522	3	Hypertrophy model	GO: 4 GO: 6355 GO: 6350	GO: 5488 GO: 4879	GO: 5634

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
						GO: 46872 GO: 3707 GO: 4887 GO: 3700 GO: 8270	
miR-372	OSBPL8	Hs.430849	3		GO: 6869 GO: 8202		
miR-372	PAPOLA	Hs.253726	3	mRNA processing			
miR-372	PCAF	Hs.533055	3				
miR-372	PCDHA4	Hs.199343	3				
miR-372	PERQ1	Hs.414396	3				
miR-372	PHF1	Hs.166204	3		GO: 6355	GO: 46872 GO: 3676 GO: 5515 GO: 3700 GO: 8270	GO: 5634
miR-372	PHF2	Hs.211441	3		GO: 6355	GO: 46872 GO: 5515 GO: 3700 GO: 8270	GO: 5634
miR-372	PLAG1	Hs.14968	3			GO: 46872 GO: 3676 GO: 3700 GO: 8270	GO: 5634
miR-372	PLAGL2	Hs.154104	3		GO: 6355 GO: 6350	GO: 46872 GO: 3700 GO: 8270	GO: 5634
miR-372	POLK	Hs.135756	3	DNA polymerase 03030	GO: 6281 GO: 6260 GO: 6280	GO: 3677 GO: 3887 GO: 287 GO: 16740 GO: 8270	GO: 5634
miR-372	POLQ	Hs.241517	3	Purine metabolism; Pyrimidine metabolism; DNA polymerase			
miR-372	PPP3CA	Hs.435512	3	Amyotrophic lateral sclerosis 05030; Apoptosis 04210; Axon guidance 04360; B cell receptor signaling pathway 04662; Calcium signaling pathway 04020; MAPK signaling pathway	GO: 6470	GO: 5509 GO: 5516 GO: 16787 GO: 5506 GO: 4722 GO: 8270	GO: 5955 GO: 5634
miR-372	PPP3CA	Hs.535457	3	G Protein Signaling; Calcium signaling pathway			
miR-372	PPP6C	Hs.495128	3		GO: 82 GO: 6470	GO: 16787 GO: 5506 GO: 30145 GO: 46872 GO: 4722	
miR-372	PRDM4	Hs.506655	3		GO: 8283 GO: 6355 GO: 7165 GO: 6350 GO: 6366	GO: 3677 GO: 3702 GO: 46872 GO: 8270	GO: 5634
miR-372	PRRX1	Hs.283416	3				
miR-372	PUM1	Hs.144795	3		GO: 6812 GO: 6936 GO: 7269 GO: 6813 GO: 7268	GO: 5509 GO: 15269 GO: 287 GO: 30955 GO: 5515 GO: 5249	GO: 16021 GO: 16020 GO: 8076
miR-372	RAB11A	Hs.321541	3				
miR-372	RAB6A	Hs.503222	3		GO: 6888 GO: 15031 GO: 7264	GO: 5525 GO: 3924 GO: 166 GO: 5515	GO: 5795
miR-372	RAB6C	Hs.535586	3		GO: 6886 GO: 42493 GO: 7264	GO: 5525 GO: 3924 GO: 166	GO: 5622

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
miR-372	RAB7	Hs.15738	3		GO: 6897 GO: 6886 GO: 7264		
miR-372	RAB7B	Hs.534612	3		GO: 6886 GO: 7264	GO: 5525 GO: 166	GO: 5764
miR-372	RABGAP1	Hs.271341	3				
miR-372	RALGDS	Hs.106185	3		GO: 7264	GO: 5085	GO: 8372
miR-372	RBL2	Hs.513609	3	Cell cycle 04110; TGF-beta signaling pathway 04350	GO: 7049 GO: 45786 GO: 6355 GO: 6350	GO: 3677 GO: 5515	GO: 5634
miR-372	RBM17	Hs.498548	3	mRNA processing			
miR-372	RDBP	Hs.423935	3	Gene Expression 74160; Transcription 74159	GO: 4 GO: 6355 GO: 6350	GO: 3723 GO: 166 GO: 5515	GO: 5634
miR-372	RGL1	Hs.497148	3		GO: 7264	GO: 8321 GO: 5515	GO: 8372
miR-372	RHOC	Hs.514941	3				
miR-372	RPS6KA1	Hs.149957	3	Ribosomal Proteins; Calcium signaling pathway; Phosphatidylinositol signaling system	GO: 6468 GO: 7165	GO: 5524 GO: 166 GO: 4672 GO: 4674 GO: 4713 GO: 3735 GO: 16740	
miR-372	RPS6KA5	Hs.510225	3	MAPK signaling pathway 04010	GO: 7173 GO: 16572 GO: 6468 GO: 7243 GO: 6508 GO: 6355 GO: 422	GO: 5524 GO: 3824 GO: 8237 GO: 166 GO: 5515 GO: 4674 GO: 4713 GO: 16740	GO: 5634
miR-372	RSBN1	Hs.486285	3				
miR-372	RTN1	Hs.368626	3		GO: 30182 GO: 7165	GO: 5554 GO: 4871	GO: 5783 GO: 30176 GO: 16021
miR-372	RUNX1	Hs.149261	3		GO: 7275 GO: 45944 GO: 6355 GO: 6350	GO: 5524 GO: 5515 GO: 3700 GO: 16563	GO: 5634
miR-372	SAR1B	Hs.432984	3		GO: 6888 GO: 6886 GO: 7264	GO: 5525 GO: 287 GO: 166	GO: 5795 GO: 5783 GO: 16020
miR-372	SART1	Hs.502883	3				GO: 5829
miR-372	SENP1	Hs.371957	3		GO: 6508 GO: 6512	GO: 8234 GO: 4175	GO: 5634
miR-372	SLC2A4	Hs.380691	3	Adipocytokine signaling pathway 04920; Insulin signaling pathway 04910; Type II diabetes mellitus 04930; Metabolism of sugars 71387	GO: 5975 GO: 8643 GO: 42593 GO: 15758	GO: 5355 GO: 5515 GO: 5351 GO: 5215	GO: 9897 GO: 5887 GO: 16020 GO: 5624 GO: 48471 GO: 12506
miR-372	SLITRK3	Hs.101745	3				GO: 16021
miR-372	STAT3	Hs.463059	3	Adipocytokine signaling pathway 04920; Jak-STAT signaling pathway 04630	GO: 7259 GO: 6953 GO: 6928 GO: 19221 GO: 7242 GO: 122	GO: 5509 GO: 5062 GO: 4871 GO: 3700 GO: 8134	GO: 5737 GO: 5634
miR-372	SUV39H1	Hs.522639	3	Lysine degradation 00310	GO: 67 GO: 6333 GO: 16568	GO: 8757 GO: 3682 GO: 46974 GO: 18024 GO: 5515 GO: 167	GO: 785 GO: 794 GO: 5634
miR-372	SUV420H1	Hs.503001	3				
miR-372	TIPARP	Hs.12813	3				
miR-372	TP53INP2	Hs.516994	3				
miR-372	TRPS1	Hs.253594	3		GO: 6607 GO: 6355 GO: 1501	GO: 46872 GO: 3700 GO: 8270	GO: 5634

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
					GO: 6350 GO: 6366		
miR-372	TRPV6	Hs.302740	3				
miR-372	TUSC2	Hs.517981	3				
miR-372	UBE2B	Hs.385986	3	Ubiquitin mediated proteolysis	GO: 6281 GO: 6512	GO: 16874 GO: 8642 GO: 4842	GO: 16020 GO: 5634
miR-372	VLDLR	Hs.370422	3		GO: 8203 GO: 6897 GO: 6629 GO: 6869 GO: 7613 GO: 7399 GO: 7165 GO: 8202	GO: 5509 GO: 5319 GO: 5041 GO: 4872	GO: 5905 GO: 16021 GO: 16020 GO: 5624
miR-372	YWHAZ	Hs.492407	3	Cell cycle 04110		GO: 19904	
miR-372	ZBTB4	Hs.35096	3				
miR-372	ZDHHC17	Hs.4014	3		GO: 42953 GO: 43123	GO: 8415 GO: 46872 GO: 5515 GO: 19706 GO: 4871 GO: 16740 GO: 8270	GO: 5795 GO: 16021 GO: 16020
miR-372	ZNF238	Hs.69997	3		GO: 7001) GO: 122 GO: 6355 GO: 6350 GO: 6810	GO: 46872 GO: 3676 GO: 5515 GO: 3704 GO: 3700 GO: 8270	GO: 228 GO: 5634
miR-372	ZNF385	Hs.505653	3				
miR-372	ZNF532	Hs.529023	3			GO: 3677 GO: 46872 GO: 8270	GO: 5634
miR-372	PRDM8	Hs.373642	3		GO: 6355 GO: 6350	GO: 3677 GO: 46872 GO: 3676 GO: 8270	GO: 5634
miR-372	DDOST	Hs.523145	3	N-Glycan biosynthesis 00510	GO: 18279	GO: 4579 GO: 16740	GO: 5789 GO: 16021
miR-372	ZFP91	Hs.524920	3				
miR-372	FBXL4	Hs.536850	3		GO: 6512 GO: 6511		GO: 5634 GO: 151
miR-221	PHF1	Hs.166204	5		GO: 6355	GO: 46872 GO: 3676 GO: 5515 GO: 3700 GO: 8270	GO: 5634
miR-221	PHF2	Hs.211441	5		GO: 6355	GO: 46872 GO: 5515 GO: 3700 GO: 8270	GO: 5634
miR-221	ATP1A4	Hs.367953	5	Calcium regulation in cardiac cells	GO: 15991 GO: 6812 GO: 30641 GO: 8152 GO: 6813 GO: 6814 GO: 30317	GO: 5524 GO: 15662 GO: 3824 GO: 16787 GO: 16820 GO: 287 GO: 15077 GO: 166 GO: 30955 GO: 31402 GO: 5391	GO: 16020 GO: 5890
miR-221	ZNF385	Hs.505653	5				
miR-221	TCF12	Hs.511504	5		GO: 7275 GO: 6955 GO: 7517 GO: 45449 GO: 6357	GO: 3677 GO: 3702 GO: 30528	GO: 5634
miR-221	MESDC1	Hs.513071	5				
miR-221	KHDRBS2	Hs.519794	5				

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
miR-221	C20orf23	Hs.101774	4		GO: 7242 GO: 7018	GO: 5524 GO: 3777 GO: 166	GO: 5874 GO: 5875
miR-221	SLC25A37	Hs.122514	4				
miR-221	MAPK10	Hs.125503	4	Apoptosis; Apoptosis; G13 Signaling Pathway; Integrin-mediated cell adhesion; MAPK Cascade; Wnt signaling			
miR-221	ARF4	Hs.148330	4	Cholera - Infection 05110	GO: 6888 GO: 6886 GO: 7264	GO: 5525 GO: 3924 GO: 8047 GO: 166	GO: 5795
miR-221	VAPB	Hs.182625	4		GO: 6461	GO: 5554 GO: 5198	GO: 5887
miR-221	DMRT3	Hs.189174	4				
miR-221	PCDHA6	Hs.199343	4		GO: 7155 GO: 7156 GO: 7399	GO: 5509 GO: 5515	GO: 5887 GO: 16020
miR-221	NLK	Hs.208759	4				
miR-221	FOS	Hs.25647	4	B cell receptor signaling pathway 04662; MAPK signaling pathway 04010; T cell receptor signaling pathway 04660; Toll-like receptor signaling pathway 04620	GO: 6306 GO: 6954 GO: 6357	GO: 3677 GO: 3704	GO: 5634
miR-221	DHDDS	Hs.369385	4	N-Glycan biosynthesis 00510	GO: 8152	GO: 16740	
miR-221	ATP1A1	Hs.371889	4		GO: 15991 GO: 6812 GO: 30641 GO: 8152 GO: 6813 GO: 6814 GO: 30317	GO: 5524 GO: 15662 GO: 16787 GO: 16820 GO: 287 GO: 15077 GO: 166 GO: 30955 GO: 5515 GO: 31402 GO: 5391	GO: 16020 GO: 5624 GO: 5890
miR-221	MGC16179	Hs.371889	4				
miR-221	ANKHD1	Hs.434219	4				
miR-221	PAK1	Hs.435714	4	Integrin-mediated cell adhesion			
miR-221	IRX5	Hs.435730	4		GO: 6355	GO: 3700	GO: 5634
miR-221	PKN1	Hs.466044	4	G13 Signaling Pathway	GO: 7257 GO: 6468 GO: 7165	GO: 5524 GO: 166 GO: 5515 GO: 4674 GO: 4713 GO: 16740	GO: 5622
miR-221	GPI	Hs.466471	4	Glycolysis/ Gluconeogenesis 00010; Pentose phosphate pathway 00030; Starch and sucrose metabolism 00500; Metabolism of sugars 71387	GO: 5975 GO: 6094 GO: 6096 GO: 7599 GO: 6959 GO: 7399	GO: 5125 GO: 4347 GO: 8083 GO: 16853	GO: 5615
miR-221	MAP3K10	Hs.466743	4	MAPK signaling pathway 04010	GO: 7257 GO: 6917 GO: 46777 GO: 7165	GO: 5524 GO: 4706 GO: 166 GO: 42803 GO: 4674 GO: 4713 GO: 16740	
miR-221	ARID1A	Hs.468972	4		GO: 30521 GO: 16568 GO: 48096 GO: 30520 GO: 42766 GO: 6355 GO: 6350	GO: 3677 GO: 5488 GO: 5515 GO: 16563	GO: 16514 GO: 5622 GO: 5634
miR-221	PDCD10	Hs.478150	4		GO: 6915		

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
miR-221	PPP6C	Hs.495128	4		GO: 82 GO: 6470	GO: 16787 GO: 5506 GO: 30145 GO: 46872 GO: 4722	
miR-221	PLEKHC1	Hs.509343	4		GO: 30036 GO: 7155 GO: 8360	GO: 5515	GO: 5856 GO: 1725
miR-221	RBM24	Hs.519904	4				
miR-221	MEIS1	Hs.526754	4		GO: 6355	GO: 3702 GO: 3700	GO: 5634
miR-221	HECTD2	Hs.535293	4		GO: 15671 GO: 6512	GO: 20037 GO: 5344 GO: 4842	GO: 5622
miR-221	GNAI2	Hs.77269	4	Axon guidance 04360; Gap junction 04540; Tight junction 04530	GO: 7186 GO: 7194 GO: 7584 GO: 7165	GO: 5525 GO: 3924 GO: 166 GO: 4871	
miR-221	CDKN1C	Hs.106070	3	Cell cycle 04110	GO: 80 GO: 7049 GO: 7050 GO: 8285 GO: 79	GO: 4861 GO: 5515	GO: 5634
miR-221	GARNL1	Hs.113150	3			GO: 5096	GO: 5634
miR-221	MIA3	Hs.118474	3		GO: 6096	GO: 166 GO: 4618	
miR-221	ARNT	Hs.131494	3		GO: 60 GO: 6355 GO: 7165	GO: 5061 GO: 5515 GO: 4872 GO: 4871 GO: 3713 GO: 3700 GO: 16563	GO: 5634
miR-221	ITGA6	Hs.133397	3	Integrin-mediated cell adhesion			
miR-221	GPRC5B	Hs.148685	3	GPCRDB Class C Metabotropic glutamate pheromone	GO: 7186 GO: 7165 GO: 7601	GO: 8067 GO: 4872 GO: 5118	GO: 16021 GO: 16020
miR-221	CDC2L6	Hs.159118	3				
miR-221	EIF5A2	Hs.164144	3				
miR-221	CD4	Hs.17483	3	Cell adhesion molecules 04514; Hematopoietic cell lineage 04640; T cell receptor signaling pathway 04660	GO: 30217 GO: 45058 GO: 7155 GO: 6955 GO: 45086 GO: 7169	GO: 42289 GO: 15026 GO: 5515 GO: 4888 GO: 8270	GO: 42101 GO: 16021 GO: 5886
miR-221	GABRA1	Hs.175934	3	Neuroactive ligand-receptor interaction 04080	GO: 6821 GO: 7214 GO: 6811	GO: 4890 GO: 5230 GO: 5216 GO: 30594	GO: 5887 GO: 45211
miR-221	C1QDC1	Hs.234355	3				
miR-221	CDKN1B	Hs.238990	3	Cell cycle 04110	GO: 7050 GO: 8285 GO: 79	GO: 4861 GO: 5515 GO: 5072	GO: 5737 GO: 5634
miR-221	TRPS1	Hs.253594	3		GO: 6607 GO: 6355 GO: 1501 GO: 6350 GO: 6366	GO: 46872 GO: 3700 GO: 8270	GO: 5634
miR-221	DNAJC14	Hs.253844	3				
miR-221	PGGT1B	Hs.254006	3		GO: 18348	GO: 4662 GO: 46872 GO: 4659 GO: 16740 GO: 8270	GO: 5953
miR-221	MYO1C	Hs.286226	3			GO: 5524 GO: 3779 GO: 5516 GO: 3774 GO: 166	GO: 16459 GO: 16461
miR-221	SEC24B	Hs.292472	3		GO: 6888 GO: 6886 GO: 16192	GO: 5515 GO: 5215	GO: 30127 GO: 5795 GO: 5783 GO: 16020

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
miR-221	RAB1A	Hs.310645	3		GO: 6888 GO: 15031 GO: 7264	GO: 5525 GO: 166	GO: 5795 GO: 5783
miR-221	ASB7	Hs.31845	3		GO: 7242		
miR-221	LOC145758	Hs.31845	3				
miR-221	ZFHX1B	Hs.34871	3	TGF Beta Signaling Pathway			
miR-221	HRB	Hs.352962	3		GO: 6406 GO: 43087 GO: 6810	GO: 3677 GO: 3723 GO: 46872 GO: 5515 GO: 8270	GO: 5643 GO: 5634
miR-221	EXOC8	Hs.356198	3				
miR-221	CTCF	Hs.368367	3		GO: 45786 GO: 122 GO: 45893 GO: 6350	GO: 3702 GO: 46872 GO: 3676 GO: 3714 GO: 3700 GO: 8270	GO: 5634
miR-221	MYO1E	Hs.370392	3		GO: 30048	GO: 5524 GO: 42623 GO: 3779 GO: 5516 GO: 146 GO: 166	GO: 16459
miR-221	PRDM2	Hs.371823	3		GO: 6355	GO: 46872 GO: 3676 GO: 3700 GO: 8270	GO: 5634
miR-221	APG7L	Hs.373959	3				
miR-221	ATG7	Hs.373959	3				
miR-221	VGLL4	Hs.373959	3		GO: 6355 GO: 6350		GO: 5634
miR-221	IRF2	Hs.374097	3	Apoptosis	GO: 8283 GO: 6955 GO: 122 GO: 6355 GO: 6350	GO: 3702 GO: 3700	GO: 5634
miR-221	DAPK1	Hs.380277	3		GO: 6915 GO: 8624 GO: 6468 GO: 7243 GO: 7165	GO: 5524 GO: 4685 GO: 5516 GO: 4684 GO: 166 GO: 4674 GO: 16740	GO: 15629
miR-221	BMF	Hs.386140	3	Apoptosis 109581	GO: 6915	GO: 5515	GO: 16459
miR-221	PAIP2	Hs.396644	3		GO: 45947 GO: 6445	GO: 5515 GO: 30371	GO: 5737
miR-221	EIF3S1	Hs.404056	3	Gene Expression 74160; Translation 72766	GO: 6412 GO: 6446	GO: 5515 GO: 3743	GO: 5852
miR-221	OGT	Hs.405410	3	Blood group glycolipid biosynthesis-lactoseries 00601; Blood group glycolipid biosynthesis-neolactoseries 00602; Fructose and mannose metabolism 00051; Ganglioside biosynthesis 00604; Globoside metabolism 00603; Glycerolipid metabolism 00561; Glycosphingolipid metabolism 00600; High-mannose type N-glycan biosynthesis 00513; N-Glycan biosynthesis 00510; O-Glycan biosynthesis 00512	GO: 6493 GO: 7584 GO: 7165	GO: 8375 GO: 5488 GO: 5515 GO: 16757	GO: 5829 GO: 5634
miR-221	CPNE8	Hs.40910	3				
miR-221	PBX3	Hs.428027	3		GO: 7387 GO: 9790 GO: 30902	GO: 5515 GO: 3700	GO: 5634

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
miR-221	ZFPM2	Hs.431009	3		GO: 7388 GO: 6355 GO: 45898 GO: 6357 GO: 6350	GO: 3677 GO: 3702 GO: 46872 GO: 3714 GO: 8270	GO: 5634
miR-221	ANKHD1	Hs.434219	3	Translation Factors			
miR-221	RIMS3	Hs.434924	3		GO: 6887 GO: 6836		GO: 45202
miR-221	ATXN1	Hs.434961	3			GO: 3723	GO: 5737 GO: 5634
miR-221	EPB41L1	Hs.437422	3				
miR-221	POLH	Hs.439153	3			GO: 3723	GO: 5737 GO: 5634
miR-221	HOXC10	Hs.44276	3		GO: 9653 GO: 8284 GO: 6355	GO: 3702 GO: 3700	GO: 5634
miR-221	Transcribed locus	Hs.446484	3				
miR-221	IQCK	Hs.460217	3				
miR-221	OSBPL7	Hs.463320	3		GO: 6869 GO: 8202	GO: 3676	
miR-221	DOCK10	Hs.46578	3			GO: 5525 GO: 51020 GO: 5488 GO: 5085 GO: 4872	
miR-221	MYO10	Hs.481720	3		GO: 7165	GO: 5524 GO: 3779 GO: 3774 GO: 166	GO: 5856 GO: 16459
miR-221	PAIP1	Hs.482038	3	Translation Factors	GO: 48255 GO: 45946 GO: 6413	GO: 3723 GO: 5515 GO: 8494	GO: 5737
miR-221	PAIP1	Hs.482038	3	Translation Factors			
miR-221	MYLIP	Hs.484738	3	Tryptophan metabolism 00380	GO: 6928 GO: 7399 GO: 16567	GO: 8092 GO: 16874 GO: 46872 GO: 4842 GO: 8270	GO: 5737 GO: 5856 GO: 16020 GO: 151
miR-221	POGZ	Hs.489873	3		GO: 7275	GO: 3677 GO: 46872 GO: 3676 GO: 8270	GO: 5634
miR-221	VDAC3	Hs.491597	3	Calcium signaling pathway 04020	GO: 15853 GO: 6820	GO: 15482 GO: 8308	GO: 5887 GO: 5741 GO: 5739
miR-221	PLS3	Hs.496622	3			GO: 3779 GO: 5509 GO: 5515	GO: 15629
miR-221	NAV1	Hs.497369	3		GO: 6306 GO: 6810	GO: 5524 GO: 3677 GO: 17111 GO: 166	
miR-221	KCNK2	Hs.497745	3		GO: 6811 GO: 6813	GO: 3824 GO: 5216 GO: 15271 GO: 5267 GO: 30955 GO: 5244	GO: 16021 GO: 16020
miR-221	INA	Hs.500916	3				
miR-221	GALNTL4	Hs.501911	3	O-Glycan biosynthesis 00512		GO: 5509 GO: 30145 GO: 4653 GO: 5529 GO: 16740 GO: 16757	GO: 5795 GO: 16021
miR-221	QKI	Hs.510324	3			GO: 3676	
miR-221	YWHAG	Hs.520974	3	Cell cycle 04110	GO: 7010 GO: 43066 GO: 6469	GO: 3779 GO: 5159 GO: 19904	GO: 5737

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
					GO: 7088 GO: 45664 GO: 9966 GO: 48167	GO: 42803 GO: 5080 GO: 8426	
miR-221	ANGPTL2	Hs.521731	3		GO: 7275	GO: 5102	GO: 5615
miR-221	TP53BP2	Hs.523968	3		GO: 6915 GO: 74 GO: 7165	GO: 5070 GO: 5515	GO: 5737
miR-221	VASH1	Hs.525479	3		GO: 7049 GO: 7050		
miR-221	PPARGC1A	Hs.527078	3	Adipocytokine signaling pathway 04920; Insulin signaling pathway 04910	GO: 8380 GO: 30521 GO: 50873 GO: 1678 GO: 45333 GO: 7586 GO: 19395 GO: 6094 GO: 6397 GO: 7005 GO: 46321 GO: 45722 GO: 35066 GO: 45893 GO: 6461 GO: 50821 GO: 42594 GO: 1659 GO: 6350 GO: 6367	GO: 3677 GO: 3723 GO: 16455 GO: 50681 GO: 30374 GO: 166 GO: 8134	GO: 5665 GO: 5634
miR-221	SOCS3	Hs.527973	3	Adipocytokine signaling pathway 04920; Insulin signaling pathway 04910; Jak-STAT signaling pathway 04630; Type II diabetes mellitus 04930	GO: 7259 GO: 6916 GO: 7242 GO: 9968 GO: 1558	GO: 4860	
miR-221	HIPK1	Hs.532363	3		GO: 6468 GO: 6355 GO: 6350	GO: 5524 GO: 16301 GO: 166 GO: 5515 GO: 4674 GO: 16740	GO: 5634
miR-221	GNB3	Hs.534315	3	Energy Metabolism 163685	GO: 7186 GO: 8217 GO: 7165	GO: 3924 GO: 4871	GO: 5834
miR-221	TFR2	Hs.544932	3		GO: 6879 GO: 6826 GO: 6508	GO: 8233 GO: 4872 GO: 4998	GO: 5887
miR-221	SLC4A4	Hs.5462	3		GO: 6820 GO: 6810	GO: 5452 GO: 8510	GO: 16021 GO: 5887 GO: 16020
miR-221	MAGI1	Hs.567389	3	Dentatorubropallidoluysian atrophy 05050; Tight junction 04530	GO: 7155 GO: 7166 GO: 6461	GO: 5524 GO: 16301 GO: 166 GO: 8022 GO: 16740	GO: 5886 GO: 5923
miR-221	PAIP1	Hs.567929	3	Translation Factors			
miR-221	ADAM11	Hs.6088	3		GO: 7229 GO: 6508	GO: 5178 GO: 4222	GO: 16021 GO: 5886
miR-221	RALA	Hs.6906	3		GO: 6935 GO: 6886 GO: 7165 GO: 7264	GO: 5525 GO: 166 GO: 5515	
miR-221	PSMD8	Hs.78466	3	Proteasome 03050; Cell Cycle 69278; Cell Cycle Checkpoints 69620; DNA Replication 69306	GO: 6508 GO: 74		GO: 5829 GO: 5838)
miR-221	ANGPTL4	Hs.9613	3		GO: 1525 GO: 30154 GO: 9267 GO: 43066 GO: 51005 GO: 45766	GO: 4857	GO: 5576

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
					GO: 45834 GO: 1666		
miR-221	FAM13A1	Hs.97270	3				
miR-221	NTF3	Hs.99171	3	MAPK signaling pathway 04010	GO: 6916 GO: 6928 GO: 7267 GO: 7399 GO: 7165	GO: 8083	
miR-221	RSBN1L	Hs592289	3				
miR-137	SON	Hs.517262	5		GO: 6916	GO: 3677 GO: 3725 GO: 3676	GO: 8372 GO: 5622 GO: 5634
miR-137	ARID4B	Hs.533633	4			GO: 3677 GO: 3676	GO: 5622
miR-137	CA7	Hs.37014	4	Nitrogen metabolism 00910	GO: 6730	GO: 4089 GO: 16829 GO: 46872 GO: 8270	
miR-137	CADPS	Hs.127013	4		GO: 6887		GO: 5829
miR-137	CLPX	Hs.113823	4		GO: 6457 GO: 15031	GO: 5524 GO: 42623 GO: 46872 GO: 166 GO: 51082 GO: 8270	GO: 5739
miR-137	COCH	Hs.21016	4		GO: 7605		
miR-137	CPNE8	Hs.40910	4				
miR-137	CPSF6	Hs.369606	4		GO: 6397	GO: 3723 GO: 166	GO: 5634
miR-137	DHX40	Hs.29403	4				
miR-137	DUSP4	Hs.417962	4	MAPK signaling pathway 04010	GO: 165 GO: 6470 GO: 74	GO: 17017 GO: 16787 GO: 4725 GO: 8330	GO: 5634
miR-137	EPHA7	Hs.73962	4	Axon guidance 04360	GO: 6468 GO: 7169	GO: 5524 GO: 5003 GO: 166 GO: 5515 GO: 4872 GO: 16740	GO: 16021 GO: 16020
miR-137	ESRRA	Hs.110849	4	Nuclear Receptors	GO: 6355 GO: 6350	GO: 46872 GO: 5496 GO: 3707 GO: 3700 GO: 8270	GO: 5634
miR-137	FKBP4	Hs.524183	4	Calcium signaling pathway	GO: 6457	GO: 5528 GO: 16853 GO: 3755 GO: 30674	GO: 5737 GO: 5634
miR-137	FURIN	Hs.513153	4	Notch Signaling Pathway 157118; Post-translational modification of proteins 163841	GO: 7267 GO: 6508	GO: 5509 GO: 4276 GO: 8233 GO: 4289	GO: 5794 GO: 16021 GO: 30140
miR-137	HLF	Hs.196952	4		GO: 7275 GO: 6355 GO: 48511 GO: 6350 GO: 6366	GO: 3690	GO: 5634
miR-137	HMGN3	Hs.77558	4		GO: 4	GO: 3677 GO: 46966	GO: 785 GO: 5634
miR-137	INPP5A	Hs.523360	4	Inositol phosphate metabolism 00562; Phosphatidylinositol signaling system 04070	GO: 7154	GO: 16787 GO: 4437 GO: 4445	GO: 16020
miR-137	NMNAT3	Hs.208673	4				
miR-137	NY-SAR-41	Hs.348418	4				
miR-137	PPP3CB	Hs.500067	4	Apoptosis 04210; Axon guidance 04360; B cell receptor signaling pathway 04662; Calcium signaling pathway	GO: 6470 GO: 74 GO: 7165 GO: 6351	GO: 5509 GO: 5516 GO: 16787 GO: 5506 GO: 4722	GO: 5955

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
				04020; MAPK signaling pathway 04010; Natural killer cell mediated cytotoxicity 04650; T cell receptor signaling pathway 04660; Wnt signaling pathway 04310		GO: 8270	
miR-137	PTPN2	Hs.123352	4	Calcium signaling pathway; Type I diabetes mellitus	GO: 6470	GO: 16787 GO: 4725 GO: 4872	
miR-137	SYT1	Hs.310545	4				
miR-137	TDRD7	Hs.193842	4				
miR-137	WIF1	Hs.284122	4	Wnt signaling pathway 04310	GO: 16055 GO: 7267 GO: 7275 GO: 7165	GO: 4713	
miR-137	ZC3H6	Hs.190477	4				
miR-137	ABHD6	Hs.476454	3		GO: 6725	GO: 16787	
miR-137	ACSL6	Hs.14945	3	Adipocytokine signaling pathway 04920; Fatty acid metabolism 00071	GO: 6637 GO: 6629 GO: 8152	GO: 16874 GO: 4467 GO: 287	GO: 16021 GO: 5792 GO: 5741 GO: 5778 GO: 5886
miR-137	ACVR1	Hs.470316	3	Cytokine-cytokine receptor interaction 04060; TGF-beta signaling pathway 04350	GO: 6468 GO: 7178	GO: 5524 GO: 287 GO: 30145 GO: 166 GO: 4713 GO: 4872 GO: 16740 GO: 5024	GO: 5887 GO: 16020
miR-137	AP3S1	Hs.406191	3		GO: 8286 GO: 6886 GO: 6810	GO: 5215	GO: 5795 GO: 30125 GO: 30119 GO: 30133
miR-137	ATBF1	Hs.569686	3				
miR-137	ATP1B1	Hs.291196	3	Calcium regulation in cardiac cells; Purine metabolism	GO: 6813 GO: 6814 GO: 6810	GO: 30955 GO: 31402 GO: 5391	GO: 16021 GO: 16020 GO: 5890
miR-137	ATXN1	Hs.434961	3				
miR-137	POLH	Hs.439153	3			GO: 3723	GO: 5737 GO: 5634
miR-137	BACH2	Hs.269764	3		GO: 6355 GO: 6350	GO: 3677 GO: 5515	GO: 5634
miR-137	C5orf13	Hs.483067	3				
miR-137	CABLES2	Hs.301040	3				
miR-137	CACNA1G	Hs.194746	3	Calcium signaling pathway 04020; Type II diabetes mellitus 04930	GO: 6816 GO: 6812	GO: 5509 GO: 5261 GO: 8332 GO: 5245	GO: 16021 GO: 16020 GO: 5624 GO: 5891
miR-137	CHES1	Hs.434286	3		GO: 77 GO: 85 GO: 6355 GO: 6350	GO: 5515 GO: 3700	GO: 5634
miR-137	CHST9	Hs.567604	3	Cysteine metabolism 00272	GO: 5975 GO: 7417 GO: 30203 GO: 42446 GO: 6790	GO: 1537 GO: 16740	GO: 5795 GO: 16021 GO: 31228
miR-137	CRSP2	Hs.407604	3		GO: 30521 GO: 45944 GO: 6350 GO: 6367	GO: 16455 GO: 30374 GO: 4872 GO: 46966 GO: 42809	GO: 119 GO: 5634
miR-137	CSDA	Hs.221889	3	Tight junction 04530	GO: 122 GO: 6355 GO: 9409 GO: 6350	GO: 3677 GO: 3702 GO: 3690 GO: 3714 GO: 3700	GO: 5737 GO: 5634
miR-137	CSE1L	Hs.90073	3		GO: 6915 GO: 8283 GO: 59 GO: 15031	GO: 5488 GO: 8262 GO: 8565	GO: 5737 GO: 5643 GO: 5634
miR-137	CUL3	Hs.372286	3	Ubiquitin mediated proteolysis 04120	GO: 82 GO: 7049 GO: 7050	GO: 5515	GO: 5634

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
					GO: 8629 GO: 8284 GO: 6512		
miR-137	DCDC2	Hs.512603	3		GO: 6968 GO: 7242 GO: 1764		
miR-137	DMRT2	Hs.59506	3		GO: 8584 GO: 6355 GO: 7530 GO: 7548 GO: 6350	GO: 46872 GO: 3700 GO: 8270	GO: 5634
miR-137	DUSP8	Hs.41688	3	MAPK signaling pathway 04010	GO: 188 GO: 6470 GO: 4725	GO: 17017 GO: 16787	GO: 5737 GO: 5634
miR-137	DYRK1A	Hs.368240	3	Benzoate degradation via CoA ligation 00632; Inositol phosphate metabolism 00562; Nicotinate and nicotinamide metabolism 00760; Phosphatidylinositol signaling system 04070	GO: 7399 GO: 18108	GO: 5524 GO: 4715 GO: 166 GO: 4674 GO: 16740	GO: 5634
miR-137	EIF2C1	Hs.22867	3		GO: 6412 GO: 6446	GO: 5515 GO: 3743	GO: 5850
miR-137	ENC1	Hs.104925	3		GO: 7275 GO: 7399	GO: 3779 GO: 5515	GO: 5856 GO: 5634
miR-137	EPAS1	Hs.468410	3		GO: 1525 GO: 30154 GO: 6355 GO: 1666 GO: 7165 GO: 6366	GO: 3705 GO: 35035 GO: 5515 GO: 4871 GO: 3713	GO: 5634
miR-137	EPHA4	Hs.371218	3	Axon guidance 04360	GO: 6468 GO: 7165 GO: 7169	GO: 5524 GO: 5003 GO: 166 GO: 4674 GO: 4872 GO: 16740	GO: 5887 GO: 16020
miR-137	ERG	Hs.473819	3		GO: 8283 GO: 7275 GO: 6468 GO: 6355 GO: 7165 GO: 6350	GO: 5515 GO: 4871 GO: 3700	GO: 5634
miR-137	ESRRG	Hs.444225	3		GO: 7275 GO: 45893 GO: 6350	GO: 50682 GO: 5516 GO: 46872 GO: 5496 GO: 3707 GO: 3700 GO: 16563 GO: 8270	GO: 5634
miR-137	FAM77C	Hs.470259	3				
miR-137	GABRA1	Hs.175934	3	Neuroactive ligand-receptor interaction 04080	GO: 6821 GO: 7214 GO: 6811	GO: 4890 GO: 5230 GO: 5216 GO: 30594	GO: 5887 GO: 45211
miR-137	GPR85	Hs.152009	3	GPCRDB Class A Rhodopsin-like	GO: 7186 GO: 7165	GO: 4872 GO: 1584	GO: 16021
miR-137	GPR88	Hs.170053	3	GPCRDB Other	GO: 7186 GO: 7165	GO: 16526 GO: 4872 GO: 1584	GO: 8372 GO: 16021
miR-137	IFT20	Hs.4187	3				GO: 19861
miR-137	ITPR3	Hs.93235	3	Calcium regulation in cardiac cells; Smooth muscle contraction			
miR-137	KIAA2010	Hs.533887	3		GO: 15986 GO: 6817	GO: 5488 GO: 46933 GO: 46961	GO: 5737 GO: 16020 GO: 16469
miR-137	LGR4	Hs.502176	3		GO: 7186 GO: 7165	GO: 16500 GO: 4872	GO: 16021
miR-137	LRRN3	Hs.3781	3				

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
miR-137	MITF	Hs.166017	3		GO: 7275 GO: 30318 GO: 6355 GO: 7605	GO: 3677 GO: 16563	GO: 5634
miR-137	MTPN	Hs.43297	3				
miR-137	MYBPC1	Hs.567306	3	Striated muscle contraction			
miR-137	NAB2	Hs.159223	3		GO: 8283 GO: 16481 GO: 7399 GO: 6355 GO: 6350	GO: 3714	GO: 5634
miR-137	NRP1	Hs.131704	3	Axon guidance 04360	GO: 1525 GO: 7411 GO: 7155 GO: 30154 GO: 7267 GO: 7399 GO: 9887 GO: 8284 GO: 7165	GO: 4872 GO: 5021	GO: 16021 GO: 16020 GO: 5624
miR-137	OXSR1	Hs.475970	3	Calcium signaling pathway; Phosphatidylinositol signaling system	GO: 6468 GO: 7243 GO: 6979	GO: 5524 GO: 287 GO: 166 GO: 5515 GO: 4674 GO: 4713 GO: 16740	
miR-137	PDLIM3	Hs.85862	3			GO: 46872 GO: 5515 GO: 8270	
miR-137	PHF15	Hs.483419	3		GO: 6355	GO: 5515 GO: 8270	
miR-137	PITPNA	Hs.429819	3		GO: 6629 GO: 6810 GO: 7601	GO: 8289 GO: 8525 GO: 8526	GO: 5622
miR-137	PLEKHA5	Hs.188614	3		GO: 4	GO: 5545	GO: 8372
miR-137	PPM1E	Hs.245044	3	; Calcium signaling pathway			
miR-137	PTGFRN	Hs.418093	3				
miR-137	RANBP2	Hs.199561	3		GO: 46907 GO: 6457 GO: 6606	GO: 8536 GO: 5488 GO: 16853 GO: 46872 GO: 3755 GO: 8270	GO: 5643 GO: 5634
miR-137	RBM12	Hs.246413	3				
miR-137	RPS13	Hs.446588	3	Ribosome 03010; Gene Expression 74160; Translation 72766	GO: 6412	GO: 3735	GO: 5840
miR-137	RWDD4A	Hs.133337	3				
miR-137	SGCG	Hs.37167	3		GO: 7010 GO: 7517		GO: 5856 GO: 16021 GO: 5886 GO: 16012
miR-137	SH3BP5	Hs.257761	3		GO: 7242	GO: 17124 GO: 5070 GO: 5515 GO: 4860	GO: 5739
miR-137	SIPA1L2	Hs.268774	3			GO: 5096 GO: 5515	
miR-137	SLC17A6	Hs.242821	3				
miR-137	SLC25A5	Hs.522767	3	Calcium signaling pathway 04020; Nucleotide metabolism 15869	GO: 6839 GO: 6810	GO: 15207 GO: 5488 GO: 5215	GO: 5887 GO: 5743 GO: 5739
miR-137	SLC43A2	Hs.160550	3				
miR-137	SLC6A15	Hs.44424	3		GO: 6836	GO: 5328 GO: 15293	GO: 5887 GO: 16020
miR-137	SLC7A9	Hs.408567	3		GO: 6520 GO: 6865 GO: 6461 GO: 6810	GO: 15184 GO: 5279	GO: 5887 GO: 5886
miR-137	SNX25	Hs.369091	3		GO: 7242	GO: 4871	

TABLE 6-continued

Predicted Target Genes of The microRNAs

microRNA	Gene Symbol	UniGene	Algorithms*	Pathways†	GO biological process	GO molecular function	GO cellular component
miR-137	SRPK1	Hs.443861	3	mRNA processing	GO: 30154 GO: 7059 GO: 398 GO: 6468 GO: 7243 GO: 50684	GO: 5524 GO: 287 GO: 166 GO: 5515 GO: 4674 GO: 16740	GO: 5737 GO: 5634
miR-137	ST18	Hs.147170	3		GO: 6355	GO: 3700	GO: 5634
miR-137	STX16	Hs.307913	3	SNARE interactions in vesicular transport 04130	GO: 6891 GO: 6886	GO: 8565 GO: 5486	GO: 5795 GO: 16021 GO: 16020 GO: 5792
miR-137	SV2A	Hs.516153	3	ECM-receptor interaction 04512	GO: 6810	GO: 15293 GO: 5215	GO: 16021 GO: 16020
miR-137	TARDBP	Hs.300624	3		GO: 7067 GO: 398 GO: 6355 GO: 6350 GO: 6366	GO: 3723 GO: 8017 GO: 166 GO: 5515 GO: 3700 GO: 5096	GO: 5634
miR-137	TBC1D19	Hs.567531	3				
miR-137	TCF12	Hs.511504	3				
miR-137	THBS4	Hs.211426	3	Cell Communication 01430; ECM-receptor interaction 04512; Focal adhesion 04510; TGF-beta signaling pathway 04350; Hemostasis 109582	GO: 7155 GO: 6930	GO: 5509 GO: 8201 GO: 5515 GO: 5198	GO: 5578)
miR-137	THRAP1	Hs.282678	3		GO: 30521 GO: 45944 GO: 6355 GO: 6350 GO: 6367	GO: 16455 GO: 30374 GO: 4872 GO: 46966 GO: 42809	GO: 119 GO: 5634
miR-137	TRPS1	Hs.253594	3		GO: 6607 GO: 6355 GO: 1501 GO: 6350 GO: 6366	GO: 46872 GO: 3700 GO: 8270	GO: 5634
miR-137	TSSK3	Hs.512763	3		GO: 30154 GO: 7242 GO: 6468 GO: 48240 GO: 7283	GO: 5524 GO: 166 GO: 4674 GO: 4713 GO: 16740	GO: 5622
miR-137	UGP2	Hs.516217	3	Galactose metabolism 00052; Nucleotide sugars metabolism 00520; Pentose and glucuronate interconversions 00040; Starch and sucrose metabolism 00500; Metabolism of sugars 71387	GO: 6011 GO: 8152	GO: 3983 GO: 16301 GO: 16740	

*Predicted by at least three of five algorithms (PicTar, TargetScan, Miranda, MirBase, and CRSD)

†Analyzed according to KEGG (http://www.genome.jp/kegg/), GenMAPP (http://www..org/), and Reactome (http://www.reactome.org/)

TABLE 7

Predicted Pathways Affected By The microRNAs

Pathway*	microRNA	No. Predicted Targets†	P value†
MAPK signaling pathway	hsa-let-7a	55	9.0E−24
	hsa-miR-372	22	5.5E−06
	hsa-miR-182*	9	3.0E−05
	hsa-miR-221	15	4.1E−04
	hsa-miR-137	13	1.7E−03

TABLE 7-continued

Predicted Pathways Affected By The microRNAs

Pathway*	microRNA	No. Predicted Targets†	P value†
Adipocytokine signaling pathway	hsa-miR-182*	6	2.7E−06
	hsa-miR-221	9	8.6E−06
	hsa-miR-137	6	1.5E−03
	hsa-miR-372	7	2.3E−03
	hsa-let-7a	6	4.2E−02

TABLE 7-continued

Predicted Pathways Affected By The microRNAs

Pathway*	microRNA	No. Predicted Targets†	P value†
VEGF signaling pathway	hsa-miR-372	11	5.2E−06
	hsa-miR-182*	5	7.0E−05
	hsa-let-7a	9	2.0E−03
	hsa-miR-137	4	4.6E−02
Wnt signaling pathway	hsa-miR-372	22	4.3E−10
	hsa-let-7a	21	8.3E−07
	hsa-miR-182*	6	3.2E−04
	hsa-miR-221	8	1.4E−02
Type II diabetes mellitus	hsa-miR-221	6	2.6E−04
	hsa-miR-137	5	1.3E−03
	hsa-let-7a	7	1.5E−03
	hsa-miR-182*	3	2.2E−03
Focal adhesion	hsa-let-7a	37	3.2E−13
	hsa-miR-182*	5	1.1E−02
	hsa-miR-221	10	1.8E−02
Adherens junction	hsa-let-7a	16	1.3E−05
	hsa-miR-221	6	3.1E−02
	hsa-miR-372	7	4.0E−02
Axon guidance	hsa-miR-137	20	3.1E−12
	hsa-let-7a	26	6.2E−11
	hsa-miR-372	19	1.4E−08
B cell receptor signaling pathway	hsa-miR-372	11	9.6E−07
	hsa-let-7a	12	4.5E−06
	hsa-miR-137	4	2.7E−02
Calcium signaling pathway	hsa-miR-372	22	1.0E−08
	hsa-let-7a	25	7.6E−08
	hsa-miR-137	11	7.5E−04
Cell cycle	hsa-miR-372	17	3.5E−09
	hsa-miR-221	9	2.4E−04
	hsa-let-7a	9	1.7E−02
ECM-receptor interaction	hsa-let-7a	27	6.0E−16
	hsa-miR-372	9	1.1E−03
	hsa-miR-182*	4	2.3E−03
Epithelial cell signaling in Helicobacter pylori infection	hsa-miR-221	7	6.1E−05
	hsa-miR-182*	4	2.0E−04
	hsa-let-7a	5	3.9E−02
Insulin signaling pathway	hsa-miR-221	9	1.6E−03
	hsa-miR-182*	4	7.8E−03
	hsa-let-7a	10	3.2E−02
Long-term potentiation	hsa-miR-372	12	1.6E−06
	hsa-let-7a	12	5.1E−05
	hsa-miR-137	5	1.5E−02

*Listed only which are regulated by at least three of five microRNAs selected in this study

†Analyzed by GeneSpring software

(f) Kaplan-Meier Survival Analysis of a 3-microRNA Signature

Applying Kaplan-Meier survival analysis, a 3-microRNA signature, composed of hsa-miR221, hsa-miR372, and hsa-miR137, was also found to be associated with patients' post-treatment survival. As shown below, this result is statistically significant.

Training Dataset (n=56):
In overall survival analysis, P value=0.0013
In relapse-free survival analysis, P value=0.0437

Testing Dataset (n=56):
In overall survival analysis, P value=0.1468
In relapse-free survival analysis, P value=0.0841

Independent Cohort (n=62):
In overall survival analysis, P value=0.0359
In relapse-free survival analysis, P value=0.0985

Training Dataset and Testing Dataset (n=112):
In overall survival, P value=0.0011
In relapse-free survival, P value=0.0119

The P values were obtained from log-rank test for testing different survival curves between high and low risk groups of patients.

Other Embodiments

All of the features disclosed in this specification may be combined in any combination. Each feature disclosed in this specification may be replaced by an alternative feature serving the same, equivalent, or similar purpose. Thus, unless expressly stated otherwise, each feature disclosed is only an example of a generic series of equivalent or similar features.

From the above description, one skilled in the art can easily ascertain the essential characteristics of the present invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. For example, compounds structurally analogous to oxadiazole compounds described above also can be made, screened for the above-described activities and used to practice this invention. Thus, other embodiments are also within the claims.

What is claimed is:

1. A method of predicting post-treatment survival of a lung cancer patient, comprising

detecting expression levels of microRNAs hsa-miR137, hsa-miR372, hsa-miR182*, hsa-miR221, and hsa-let-7a in a lung cancer patient who has been subjected to treatment;

calculating a risk score of the patient based on the expression levels of these microRNAs; and

determining prospect of post-treatment survival based on the value of the risk score.

2. The method of claim **1**, wherein the risk score is calculated as follows:

(0.15×expression level of hsa-miR137)+(0.31×expression level of hsa-miR372)+(0.28×expression level of hsa-miR182*)+(−0.13×expression level of hsa-miR221)+(−0.14×expression level of hsa-let-7a).

3. The method of claim **2**, wherein a risk score equal to or lower than −7.1 indicates that the patient has a fair prospect of post-treatment survival.

4. The method of claim **1**, wherein the patient has non-small cell lung cancer.

5. The method of claim **4**, wherein the patient is in stage I, II, or III of the non-small cell lung cancer.

6. The method of claim **1**, wherein the patient has been subjected to surgical treatment, chemical treatment, radiotherapy, or a combination thereof.

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